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STIC Search

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FILE 'REGISTRY' ENTERED AT 08:51:22 ON 13 JUN 2003
E INTERFERON ALFA/CN 5
L1 2 S E4-E5

FILE 'HCAPLUS' ENTERED AT 08:59:52 ON 13 JUN 2003
L1 2 SEA FILE=REGISTRY ABB=ON PLU=ON ("INTERFERON ALFA-2A"/CN OR "INTERFERON ALFA-2B"/CN)
L2 2097 SEA FILE=HCAPLUS ABB=ON PLU=ON L1 OR (INTERFERON OR IFN)(3A)(2A OR 2B)
L3 36 SEA FILE=HCAPLUS ABB=ON PLU=ON L2(L)((HIV1 OR HIVI OR HTLVI OR HTLV1 OR (HTLV OR HIV OR HUMAN(3W)VIRUS)(3A)(I OR 1) OR AIDS OR ACQUIRED(2W)SYNDROM?)(S)(TREAT? OR THERAP?) OR ANTIHIV1 OR ANTIHTLV1 OR ANTIHTLVI OR ANTIHIVI OR (ANTIHTLV OR ANTIHIV)(2W)(I OR 1))

L3 ANSWER 1 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:140660 HCAPLUS
DOCUMENT NUMBER: 138:302352
TITLE: Perforin expression in T cells and virological response to PEG-interferon alpha2b in HIV-1 infection
AUTHOR(S): Portales, Pierre; Reynes, Jacques; Rouzier-Panis, Regine; Baillat, Vincent; Clot, Jacques; Corbeau, Pierre
CORPORATE SOURCE: Laboratoire d'Immunologie, Hopital Saint Eloi, Montpellier, 34.295, Fr.
SOURCE: AIDS (London, United Kingdom) (2003), 17(4), 505-511
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB OBJECTIVE AND DESIGN: Interferon .alpha. (IFN.alpha.), which is known to directly inhibit the HIV-1 replicative cycle and to increase the activity of cytotoxic T lymphocytes (CTL), is being tested as an anti-HIV agent. As CTL play a major role in immune defense against HIV, the authors wanted to further characterize CTL activity and the effect of IFN.alpha. on it. METHODS: the authors followed by flow cytometry the intracellular expression of the key mediator of cytotoxicity, perforin, in peripheral blood T cells of patients treated with IFN.alpha.. RESULTS: the authors obsd. that the percentage of T cells harboring perforin was higher in infected subjects than in non-infected controls. Administration of **IFN**.alpha.**2b** attached to polyethylene glycol increased this perforin expression further and reduced viral load. The increase in the percentage of T cells expressing perforin correlated with IFN.alpha.-induced decrease in viral load. In addn., the level of perforin expression before IFN.alpha. administration was inversely correlated with viral load remaining after IFN.alpha. administration. CONCLUSION: The pre-**therapeutic** percentage of perforin-pos. T cells might be a predictive marker of the virol. response to IFN.alpha. in **HIV-1**-infected patients.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 36 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2003:128527 HCAPLUS
TITLE: Efficacy of induction therapy with high-dose interferon for patients with hemophilia and human immunodeficiency virus-hepatitis C virus coinfection
AUTHOR(S): Hanabusa, Hideji
CORPORATE SOURCE: Department of Hematology, Ogikubo Hospital, Tokyo, Japan
SOURCE: Clinical Infectious Diseases (2002), 35(12), 1527-1533
CODEN: CIDIEL; ISSN: 1058-4838
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To evaluate the efficacy of high-dose interferon (IFN) on human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection, 15 HIV-pos. patients and 15 age-matched HIV-neg. patients with hemophilia were treated with 9 million units (MU) of IFN-.alpha.2a daily for 2 wk, followed by 9 MU of IFN-.alpha.2a 3 times/wk for a further 22 wk. At week 2, HIV RNA levels decreased from 7410 .+-. 2190 to 320 .+-. 130 copies/mL, and HCV RNA levels decreased from 390 .times. 103 .+-. 80 .times. 103 to 70 .times. 103 .+-. 30 .times. 103 copies/mL in the HIV-pos. group and from 300 .times. 103 .+-. 80 .times. 103 to 10 .times. 103 .+-. 10 .times. 103 copies/mL in the HIV-neg. group. HCV RNA was undetectable after treatment in 4 of 12 HIV-pos. and 6 of 15 HIV-neg. patients. IFN therapy was discontinued because of adverse effects in 3 HIV-pos. patients. Induction therapy and the dose of IFN should be evaluated in combination therapy with IFN and ribavirin.
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:928015 HCAPLUS
DOCUMENT NUMBER: 137:379981
TITLE: HIV therapy
INVENTOR(S): Laughlin, Mark A.; Glue, Paul W.; Stalgis, Carlos O.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 14 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002182179	A1	20021205	US 2000-516673	20000301

PRIORITY APPLN. INFO.: US 1999-122370P P 19990302
US 1999-124304P P 19990312
US 1999-128296P P 19990408

AB Methods for the **treatment** of **treatment**-naive as well as **treatment**-experienced adult and pediatric patients with **HIV-1** infections as well as patients co-infected with **HIV-1** and HCV involving administration of a **therapeutically** effective amt. of

pegylated interferon-alfa, e.g., pegylated **interferon** alfa-**2b** as monotherapy or preferably in assocn. with a **therapeutically** effective amt. of at least one of ribavirin, IL-2, IL-12, pentafuside alone or in combination with a **therapeutically** effective amt. of an anti-**HIV-1** drug **therapy**, e.g., HAART are disclosed.

L3 ANSWER 4 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:828621 HCAPLUS
DOCUMENT NUMBER: 138:314544
TITLE: Oligonucleotide-mediated inhibition of hepatitis B virus and hepatitis C virus replication
INVENTOR(S): Blatt, Lawrence; Macejak, Dennis; McSwiggen, James; Morrissey, David; Pavco, Pamela; Lee, Patrice; Draper, Kenneth; Roberts, Elisabeth
PATENT ASSIGNEE(S): Ribozyme Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 387 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 50
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002081494	A1	20021017	WO 2002-XD9187	20020326
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, ML, MR, NE, SN, TD, TG				
AU 9851819	A1	19980611	AU 1998-51819	19980112
AU 729657	B2	20010208		
AU 9939188	A1	19990916	AU 1999-39188	19990713
US 2003068301	A1	20030410	US 2001-877478	20010608

PRIORITY APPLN. INFO.:

US 2001-817879	A	20010326
US 2001-296876P	P	20010608
US 2001-877478	A	20010608
US 2001-335059P	P	20011024
US 2001-337055P	P	20011205
US 1992-882712	B1	19920514
US 1994-193627	A1	19940207
AU 1995-26422	A3	19950518
US 1996-623891	A	19960325
US 1999-436430	A2	19991108
US 2000-531025	A2	20000320
US 2000-636385	A2	20000809
US 2000-696347	A2	20001024

AB The present invention relates to nucleic acid mols., including antisense and enzymic nucleic acid mols., such as hammerhead ribozymes, DNAzymes, Inozymes, Zinzymes, Amberzymes, and G-cleaver ribozymes, which modulate the synthesis, expression and/or stability

of a hepatitis C virus (HCV) or hepatitis B virus (HBV) RNA and methods for their use alone or in combination with other therapies. In addn., nucleic acid decoy mols. and aptamers that bind to HBV reverse transcriptase and/or HBV reverse transcriptase primer sequences and methods for their use alone or in combination with other therapies, are disclosed. Oligonucleotides that specifically bind the Enhancer I region of HBV DNA are further disclosed. The present invention further relates to the use of nucleic acids, such as decoy and aptamer mols. of the invention, to modulate the expression of HBV genes and HBV viral replication. Furthermore, HBV animal models and methods of use are disclosed, including methods of screening for compds. and/or potential therapies directed against HBV. The present invention also relates to compds., including enzymic nucleic acid mols., ribozymes, DNAzymes, nuclease-activating compds. and chimeras such as 2',5'-adenylates, that modulate the expression and/or replication of HCV. [This abstr. record is one of five records for this document necessitated by the large no. of index entries required to fully index the document and publication system constraints.].

L3 ANSWER 5 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:828620 HCAPLUS
DOCUMENT NUMBER: 138:117630
TITLE: Oligonucleotide-mediated inhibition of hepatitis B virus and hepatitis C virus replication
INVENTOR(S): Blatt, Lawrence; Macejak, Dennis; McSwiggen, James; Morrissey, David; Pavco, Pamela; Lee, Patrice; Draper, Kenneth; Roberts, Elisabeth
PATENT ASSIGNEE(S): Ribozyme Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 387 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 50
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002081494	A1	20021017	WO 2002-XC9187	20020326
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, ML, MR, NE, SN, TD, TG				
AU 9851819	A1	19980611	AU 1998-51819	19980112
AU 729657	B2	20010208		
AU 9939188	A1	19990916	AU 1999-39188	19990713
US 2003068301	A1	20030410	US 2001-877478	20010608

PRIORITY APPLN. INFO.:		
US 2001-817879	A	20010326
US 2001-296876P	P	20010608
US 2001-877478	A	20010608
US 2001-335059P	P	20011024

US 2001-337055P	P	20011205
US 1992-882712	B1	19920514
US 1994-193627	A1	19940207
AU 1995-26422	A3	19950518
US 1996-623891	A	19960325
US 1999-436430	A2	19991108
US 2000-531025	A2	20000320
US 2000-636385	A2	20000809
US 2000-696347	A2	20001024

AB The present invention relates to nucleic acid mols., including antisense and enzymic nucleic acid mols., such as hammerhead ribozymes, DNAzymes, Inozymes, Zinzymes, Amberzymes, and G-cleaver ribozymes, which modulate the synthesis, expression and/or stability of a hepatitis C virus (HCV) or hepatitis B virus (HBV) RNA and methods for their use alone or in combination with other therapies. In addn., nucleic acid decoy mols. and aptamers that bind to HBV reverse transcriptase and/or HBV reverse transcriptase primer sequences and methods for their use alone or in combination with other therapies, are disclosed. Oligonucleotides that specifically bind the Enhancer I region of HBV DNA are further disclosed. The present invention further relates to the use of nucleic acids, such as decoy and aptamer mols. of the invention, to modulate the expression of HBV genes and HBV viral replication. Furthermore, HBV animal models and methods of use are disclosed, including methods of screening for compds. and/or potential therapies directed against HBV. The present invention also relates to compds., including enzymic nucleic acid mols., ribozymes, DNAzymes, nuclease-activating compds. and chimeras such as 2',5'-adenylates, that modulate the expression and/or replication of HCV. [This abstr. record is one of five records for this document necessitated by the large no. of index entries required to fully index the document and publication system constraints.].

L3 ANSWER 6 OF 36 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	2002:828619 HCAPLUS
DOCUMENT NUMBER:	138:117629
TITLE:	Oligonucleotide-mediated inhibition of hepatitis B virus and hepatitis C virus replication
INVENTOR(S):	Blatt, Lawrence; Macejak, Dennis; McSwiggen, James; Morrissey, David; Pavco, Pamela; Lee, Patrice; Draper, Kenneth; Roberts, Elisabeth
PATENT ASSIGNEE(S):	Ribozyme Pharmaceuticals, Inc., USA
SOURCE:	PCT Int. Appl., 387 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	50

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002081494	A1	20021017	WO 2002-XB9187	20020326

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ,

BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, ML, MR, NE, SN, TD, TG

AU 9851819	A1	19980611	AU 1998-51819	19980112
AU 729657	B2	20010208		
AU 9939188	A1	19990916	AU 1999-39188	19990713
US 2003068301	A1	20030410	US 2001-877478	20010608

PRIORITY APPLN. INFO.:

US 2001-817879	A	20010326
US 2001-296876P	P	20010608
US 2001-877478	A	20010608
US 2001-335059P	P	20011024
US 2001-337055P	P	20011205
US 1992-882712	B1	19920514
US 1994-193627	A1	19940207
AU 1995-26422	A3	19950518
US 1996-623891	A	19960325
US 1999-436430	A2	19991108
US 2000-531025	A2	20000320
US 2000-636385	A2	20000809
US 2000-696347	A2	20001024

AB The present invention relates to nucleic acid mols., including antisense and enzymic nucleic acid mols., such as hammerhead ribozymes, DNAzymes, Inozymes, Zinzymes, Amberzymes, and G-cleaver ribozymes, which modulate the synthesis, expression and/or stability of a hepatitis C virus (HCV) or hepatitis B virus (HBV) RNA and methods for their use alone or in combination with other therapies. In addn., nucleic acid decoy mols. and aptamers that bind to HBV reverse transcriptase and/or HBV reverse transcriptase primer sequences and methods for their use alone or in combination with other therapies, are disclosed. Oligonucleotides that specifically bind the Enhancer I region of HBV DNA are further disclosed. The present invention further relates to the use of nucleic acids, such as decoy and aptamer mols. of the invention, to modulate the expression of HBV genes and HBV viral replication. Furthermore, HBV animal models and methods of use are disclosed, including methods of screening for compds. and/or potential therapies directed against HBV. The present invention also relates to compds., including enzymic nucleic acid mols., ribozymes, DNAzymes, nuclease-activating compds. and chimeras such as 2',5'-adenylates, that modulate the expression and/or replication of HCV. [This abstr. record is one of five records for this document necessitated by the large no. of index entries required to fully index the document and publication system constraints.].

L3 ANSWER 7 OF 36 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	2002:793641 HCAPLUS
DOCUMENT NUMBER:	137:320290
TITLE:	Oligonucleotide-mediated inhibition of hepatitis B virus and hepatitis C virus replication
INVENTOR(S):	Blatt, Lawrence; Macejak, Dennis; Mcswiggen, James; Morrissey, David; Pavco, Pamela; Lee, Patrice; Draper, Kenneth; Roberts, Elisabeth
PATENT ASSIGNEE(S):	Ribozyme Pharmaceuticals, Inc., USA
SOURCE:	PCT Int. Appl., 387 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 50
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002081494	A1	20021017	WO 2002-US9187	20020326
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 9851819	A1	19980611	AU 1998-51819	19980112
AU 729657	B2	20010208		
AU 9939188	A1	19990916	AU 1999-39188	19990713
US 2003068301	A1	20030410	US 2001-877478	20010608

PRIORITY APPLN. INFO.:

US 2001-817879	A	20010326
US 2001-296876P	P	20010608
US 2001-877478	A	20010608
US 2001-335059P	P	20011024
US 2001-337055P	P	20011205
US 1992-882712	B1	19920514
US 1994-193627	A1	19940207
AU 1995-26422	A3	19950518
US 1996-623891	A	19960325
US 1999-436430	A2	19991108
US 2000-531025	A2	20000320
US 2000-636385	A2	20000809
US 2000-696347	A2	20001024

OTHER SOURCE(S): MARPAT 137:320290

AB The present invention relates to nucleic acid mols., including antisense and enzymic nucleic acid mols., such as hammerhead ribozymes, DNAzymes, Inozymes, Zinzymes, Amberzymes, and G-cleaver ribozymes, which modulate the synthesis, expression and/or stability of a hepatitis C virus (HCV) or hepatitis B virus (HBV) RNA and methods for their use alone or in combination with other therapies. In addn., nucleic acid decoy mols. and aptamers that bind to HBV reverse transcriptase and/or HBV reverse transcriptase primer sequences and methods for their use alone or in combination with other therapies, are disclosed. Oligonucleotides that specifically bind the Enhancer I region of HBV DNA are further disclosed. The present invention further relates to the use of nucleic acids, such as decoy and aptamer mols. of the invention, to modulate the expression of HBV genes and HBV viral replication. Furthermore, HBV animal models and methods of use are disclosed, including methods of screening for compds. and/or potential therapies directed against HBV. The present invention also relates to compds., including enzymic nucleic acid mols., ribozymes, DNAzymes, nuclease-activating compds. and chimeras such as 2',5'-adenylates, that modulate the expression and/or replication of HCV. [This abstr. record is one of five records for this document necessitated by the large no. of index entries required to fully index the document and publication

system constraints.].
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:440921 HCAPLUS
DOCUMENT NUMBER: 137:56848
TITLE: Treatment of hepatitis C and anemia in human immunodeficiency virus-infected patients
AUTHOR(S): Dieterich, Douglas T.
CORPORATE SOURCE: New York University School of Medicine, New York, NY, USA
SOURCE: Journal of Infectious Diseases (2002), 185(Suppl. 2), S128-S137
CODEN: JIDIAQ; ISSN: 0022-1899
PUBLISHER: University of Chicago Press
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Because of shared modes of transmission, co-infection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) is common. Co-infection with HIV increases HCV virus load, liver-related mortality, and the risk of sexual and perinatal transmission of HCV, and it may accelerate HCV disease progression. With combination interferon (IFN)-.alpha.2b/ribavirin or pegylated IFN-.alpha.2b/ribavirin therapy, long-term remission is possible for HCV-infected patients. Preliminary evidence suggests that the combination of IFN-.alpha.2b/ribavirin can achieve similar response rates in HCV/HIV-co-infected individuals with no adverse effect on HIV RNA concns. Although adverse effects are more frequent with combination therapy than with IFN-.alpha. monotherapy, most are manageable. In addn., few instances of drug-drug antagonism have been reported among drugs used to treat each disease, although further study is necessary. Ribavirin-assocd. hemolytic anemia is a potential problem in a patient population that is already susceptible to anemia but is manageable with recombinant human erythropoietin (epoetin alfa).
REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:925947 HCAPLUS
DOCUMENT NUMBER: 136:193726
TITLE: Long-term efficacy of combination therapy with interferon-.alpha.2b and ribavirin for severe chronic hepatitis C in HIV-infected patients
AUTHOR(S): Landau, Alain; Batisse, Dominique; Piketty, Christophe; Van Huyen, Jean Paul Duong; Bloch, Francis; Belec, Laurent; Bruneval, Patrick; Weiss, Laurence; Jian, Raymond; Kazatchkine, Michel D.
CORPORATE SOURCE: Department of Hepatology and Gastroenterology, Hopital Europeen Georges Pompidou and Universite Pierre et Marie Curie, Paris, Fr.
SOURCE: AIDS (London, United Kingdom) (2001), 15(16), 2149-2155
CODEN: AIDSET; ISSN: 0269-9370

PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB We have assessed the long-term efficacy and safety of a combination therapy of interferon alpha-2b (IFN) and ribavirin (RBV) for the treatment of severe chronic hepatitis C in co-infected HIV-seropos. patients in an open prospective study. Fifty-one patients were treated for 12 mo. Mean baseline CD4 cell count, alanine aminotransferase and aspartate aminotransferase were 412 .+-. 232 .times. 106/I, 113 .+-. 75 IU/I and 111 .+-. 84 IU/I resp. The mean Knodell score was 11.5 .+-. 2.1 with 28 patients (55%) exhibiting histol. evidence of active cirrhosis. Fifteen (29%) patients discontinued the treatment prematurely because of adverse events. An end of treatment response (ETR) as defined by the lack of detectable hepatitis C virus (HCV) RNA in plasma at the end of treatment was achieved in 15 patients (29%). A sustained virol. response (SVR), defined by the lack of detectable HCV RNA in plasma 6 mo after completion of combination therapy, was achieved in 11 patients (21%). The HCV genotype 3a was assocd. with ETR and SVR (P = 0.002 and P = 0.003, resp.). HCV viremia at baseline was lower in patients who achieved SVR and ETR than in those who did not (6.7 .+-. 7.8 vs. 24 .+-. 26.7 .times. 106 genome equiv./mL, P = 0.03 and 14.3 .+-. 28.7 vs. 22.5 .+-. 23, P = 0.05, resp.). Our results indicate that combination therapy with IFN and RBV is effective in approx. 20% of co-infected patients with severe liver disease.
REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 10 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:849170 HCAPLUS
DOCUMENT NUMBER: 136:149500
TITLE: Low-dose IFN-.alpha. monotherapy in treatment-naive individuals with HIV-1 infection: evidence of potent suppression of viral replication
AUTHOR(S): Hatzakis, Angelos; Gargalianos, Panagiotis; Kiosses, Vassilis; Lazanas, Marios; Sypsa, Vana; Anastassopoulou, Cleo; Vigklis, Vassilios; Sambatakou, Helen; Botsi, Chrisoula; Paraskevis, Dimitris; Stalgis, Carlos
CORPORATE SOURCE: Department of Hygiene and Epidemiology, Athens University Medical School, Athens, Greece
SOURCE: Journal of Interferon and Cytokine Research (2001), 21(10), 861-869
CODEN: JICRFJ; ISSN: 1079-9907
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To evaluate the safety and antiviral action of interferon-.alpha. (IFN-.alpha.) in HIV-1 infection, the authors undertook a proof of concept study in 27 treatment-naive patients. Eligible patients comprised two groups: the IFN-.alpha.T group (n = 17), which received 5 MIU IFN-.alpha. s.c. daily for 32 consecutive days, and the IFN-.alpha.NT group (n = 10), which did not receive IFN-.alpha. prior to highly active antiretroviral therapy (HAART), which was commenced on day 28 in both groups. IFN-.alpha. treatment was well tolerated in 14 of the 17 patients of the IFN-.alpha.T group who

completed the study. The mean HIV RNA redn. in the IFN-.alpha.T group on day 14 was 1.1 log10. Viral load suppression was inversely assocd. with baseline viral load ($p = 0.031$). Four weeks after initiation of HAART, IFN-.alpha.T and IFN-.alpha.NT group patients had 2.40 and 1.82 log10 HIV RNA redn. from baseline, resp. ($p < 0.001$). There was no evidence of cross-resistance with existing antiretrovirals in patients with HIV-RNA rebound after initial plasma viral load decline .gtoreq. 1 log10 during IFN-.alpha. monotherapy. Thus, low daily IFN-.alpha. exhibits potent anti-HIV-1 activity in vivo without serious adverse effects. These properties render IFN-.alpha. an attractive candidate for further assessment as a constituent of HAART.

IT **98530-12-2**, Intron-A
RL: ADV (Adverse effect, including toxicity); DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(low-dose IFN-.alpha. monotherapy in **treatment**-naive humans with **HIV-1** infection and evidence of potent suppression of viral replication)

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:782445 HCAPLUS
DOCUMENT NUMBER: 136:79311
TITLE: Chronic hepatitis C in HIV infection: Feasibility and sustained efficacy of therapy with interferon alfa-2b and tribavirin
AUTHOR(S): Nasti, Guglielmo; Di Gennaro, Giampiero; Tavio, Marcello; Cadorin, Lucia; Tedeschi, Rosa Maria; Talamini, Renato; Carbone, Antonino; Tirelli, Umberto
CORPORATE SOURCE: Division of Oncological Medicine A, National Cancer Institute, Pordenone, Italy
SOURCE: AIDS (London, United Kingdom) (2001), 15(14), 1783-1787
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The role combination therapy with interferon alfa-2b and tribavirin (US: ribavirin) plays in producing sustained virol. responses in patients with HIV and chronic hepatitis C (HCV) infection is still unknown. Aim of this study was to det. the feasibility and sustained response of interferon alfa-2b and tribavirin combination therapy. Phase II study. Seventeen patients were enrolled at the National Cancer Institute, Aviano, Italy and received combination therapy with interferon alfa-2b 3 MIU s.c. three times a week plus tribavirin 1000-1200 mg/day for 24 wk. Antiretroviral therapy was concomitantly given in all but one patient. At the end of treatment, five (31%) patients achieved clearance of HCV RNA and 11 (69%) showed normalized liver function enzyme levels. In three patients, serum HCV RNA concn. was still undetectable 24 wk after treatment, with an overall sustained virol. response rate of 19%. The serum liver enzymes were still normal in 10 patients 24 wk after treatment, the overall sustained biochem. response rate being 62%. All patients with HCV RNA clearance at the end of treatment and 24

wk after treatment had a concomitant biochem. response. Overall the combination treatment was well tolerated. Our data confirm that the combination of interferon alfa-2b and tribavirin is well tolerated and feasible in patients with HIV-HCV co-infection and it can be assocd. safely with highly active antiretroviral therapy. The sustained response achieved with the drug combination does not seem to be any better than that achieved with 12 mo of monotherapy with interferon alfa-2b.

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 12 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:676618 HCAPLUS
DOCUMENT NUMBER: 135:225873
TITLE: HIV-specific immune response promoted by interferon-.alpha.
INVENTOR(S): Laughlin, Mark A.
PATENT ASSIGNEE(S): Schering Corporation, USA
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001066132	A2	20010913	WO 2001-US7453	20010308
WO 2001066132	A3	20020124		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002004584	A1	20020110	US 2001-801980	20010308
EP 1263457	A2	20021211	EP 2001-922303	20010308
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
NO 2002004255	A	20020906	NO 2002-4255	20020906

PRIORITY APPLN. INFO.: US 2000-188338P P 20000309
WO 2001-US7453 W 20010308

AB Use of interferon-.alpha., e.g., pegylated **interferon** .alpha.-**2a** or **2b** for prepn. of a medicament for promotion of an **HIV-1** specific immune response, e.g., promotion of **HIV-1** specific T-cells, in adult and pediatric patients having **HIV-1** infections as well as patients co-infected with **HIV-1** and HCV comprising a **therapeutically** effective amt. of pegylated interferon-.alpha., e.g., pegylated **interferon** .alpha.-**2b** is disclosed.

L3 ANSWER 13 OF 36 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:592123 HCAPLUS
DOCUMENT NUMBER: 135:342994
TITLE: Interferon alpha therapy in haemophilic patients with chronic hepatitis C: a French multicentre pilot study of 58 patients
AUTHOR(S): Beurton, Isabelle; Bertrand, Marie-Anne; Bresson-Hadni, Solange; Parquet-Gernez, Armelle; Goudemand, Jenny; Paris, Jean-Claude; Cales, Paul; Briquel, Marie-Elisabeth; Gaucher, Pierre; Cortey, Marie-Luce; Trepo, Christian; Miguet, Jean-Philippe; Cahn, Jean-Yves
CORPORATE SOURCE: Liver Diseases Unit, CHU Jean Minjoz, Besancon, F-25030, Fr.
SOURCE: European Journal of Gastroenterology & Hepatology (2001), 13(7), 859-864
CODEN: EJGHES; ISSN: 0954-691X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Background and objectives: Information about the long-term efficacy of interferon alpha (interferon-.alpha.) in hemophilic patients with chronic hepatitis not co-infected with the human immunodeficiency virus (HIV-1) is still limited. Previous studies seemed to indicate a low rate of response. The aim of this study was to evaluate the safety and long-term efficacy of interferon treatment in multi-transfused hemophiliacs. Methods: Fifty-eight hemophiliacs were scheduled to receive 3 MU of **interferon**-.alpha. **2b** three times a week for 12 mo. The patients were followed up for at least 24 mo post-treatment. Response was assessed by measurements of serum hepatitis C virus (HCV) RNA. Results: Twenty-four patients (41.4%) dropped out. Except for seven patients, the symptoms that led to interrupting interferon treatment would probably not have resulted in the same decision in non-hemophilic patients. One patient developed an inhibitor to the deficient clotting factor without hemorrhagic consequences. In an intent to treat, the sustained virol. response rate was 14%. However, when considering only the 34 patients who received the full treatment, HCV-RNA was cleared in eight patients (23%). Conclusions: This study suggests that multi-transfused hemophiliacs with chronic hepatitis not co-infected with **HIV-1** respond to prolonged **treatment** with interferon-.alpha. in a similar proportion to that obsd. in non-hemophiliacs. There was a high rate of patients who did not complete the interferon-.alpha., treatment, and this seems to be characteristic of this patient population.

REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 14 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:361053 HCAPLUS
DOCUMENT NUMBER: 135:251536
TITLE: The combination of zidovudine and interferon alpha-2B in the treatment of adult T-cell leukemia/lymphoma
AUTHOR(S): White, Jeffrey D.; Wharfe, Gilian; Stewart, Donn M.; Maher, Virginia E.; Eicher, Donald; Herring, Bert; Derby, Michael; Jackson-Booth, Peta-Gay;

Marshall, Margaret; Lucy, Daniel; Jain, Ashish; Cranston, Beverley; Hanchard, Barrie; Lee, Cathryn C.; Top, Lois E.; Fleisher, Thomas A.; Nelson, David L.; Waldmann, Thomas A.

CORPORATE SOURCE: Metabolism Branch, National Cancer Institute, University of the West Indies, Kingston, Jamaica

SOURCE: Leukemia & Lymphoma (2001), 40(3/4), 287-294
CODEN: LELYEA; ISSN: 1042-8194

PUBLISHER: Harwood Academic Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Adult T-cell leukemia/lymphoma (ATL) is frequently a very aggressive malignancy with a poor survival despite aggressive multi-agent chemotherapy. The combination of the antiretroviral drug zidovudine (AZT) and interferon alpha (IFN.alpha.) has been reported to induce remissions in patients with ATL. The purpose of this study was to evaluate the clin. response and toxicity following administration of a combination of IFN.alpha.-2b and AZT in patients with human T-cell lymphotropic virus type 1 (HTLV-1)-assocd. ATL. Eighteen patients with ATL (chronic, crisis, acute or lymphoma type) were treated with the combination of AZT (50-200 mg orally 5 times a day) and IFN.alpha.-2b (2.5-10 million units s.c. daily). Three patients had objective responses lasting more than one month. One patient had a clin. complete remission, lasting 21.6 mo and two patients had partial remissions lasting 3.7 and 26.5 mo. Six patients were not considered evaluable for response due to short and/or interrupted periods of treatment. Seventeen patients have died with a median survival time after initiation of therapy of 6 mo. Neutropenia and thrombocytopenia were the dose limiting toxicities. In conclusion, the response rate in this study was lower than noted in the two previous published series. This may be due to the amt. and type of prior treatment the authors' patients had received.

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 15 OF 36 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:628016 HCAPLUS

DOCUMENT NUMBER: 133:206775

TITLE: HIV therapy using pegylated interferon-alfa alone and in assocn. with anti-HIV-1 drug therapy

INVENTOR(S): Laughlin, Mark A.; Glue, Paul W.; Stalgis, Carlos O.

PATENT ASSIGNEE(S): Schering Corporation, USA

SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000051631	A2	20000908	WO 2000-US5361	20000301
WO 2000051631	A3	20010118		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN,

IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

JP 2000256211	A2	20000919	JP 2000-55695	20000301
EP 1034790	A2	20000913	EP 2000-301695	20000302
EP 1034790	A3	20001213		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO

PRIORITY APPLN. INFO.:

US 1999-260388	A2 19990302
US 1999-268521	A2 19990312
US 1999-288358	A2 19990408
US 1999-454004	A2 19991203

AB The uses of pegylated interferon-alfa, alone, and in assocn. with an anti-**HIV-1** drug **therapy**, and ribavirin for the prepn. of a medicament for **treating** **treatment**-naive as well as **treatment**-experienced adult and pediatric patients having **HIV-1** infections as well as patients co-infected with **HIV-1** and hepatitis C virus (HCV) involving comprising a **therapeutically** effective amt. of pegylated interferon-alfa, e.g., pegylated **interferon** alfa-**2b** as monotherapy or preferably in assocn. with a **therapeutically** effective amt. of at least one of ribavirin, IL-2, IL-12, pentafuside alone or in combination with a **therapeutically** effective amt. of an anti-**HIV-1** drug **therapy**, e.g., HAART are disclosed.

IT **77907-69-8D**, **Interferon**-alfa **2a**, pegylated **98530-12-2D**, **Interferon**-alfa **2b**, pegylated
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**HIV-1 therapy** using pegylated interferon-alfa alone and in assocn. with anti-**HIV-1** drug **therapy** in relation to hepatitis C virus **therapy**)

L3 ANSWER 16 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:460052 HCAPLUS
DOCUMENT NUMBER: 133:72678
TITLE: Does HIV-infection influence the response of chronic hepatitis C to interferon treatment? A French multicenter prospective study
AUTHOR(S): Causse, Xavier; Payen, Jean-Louis; Izopet, Jacques; Babany, Gerard; Girardin, Marie-France Saint-Marc; Bailly, F.; Housset, C.; Tran, A.; Pariente, A.; Lagasse, J. P.; Desmorat, H.; Bettan, L.; Bloch, F.; Couzigou, P.; Chossegros, P.; Laurent Puig, P.; Bacq, Y.; Douvin, C.; Raabe, J. J.; Van Lemmens, C.; Zarski, J. P.; Bernard, P.; Rozenbaum, W.; Trois Vallets, D.; Fischer, D.; Sogni, P.; Boucher, E.; Boyer, N.; Lang, J. M.; Danne, O.; Barbare, J. C.; Force, G.; Schmit, J. C.; Mesnard, B.; Gauthier, A.;

Poveda, J. D.; Sayada, C.; Olivares, R.; Montestruc, F.
CORPORATE SOURCE: Orleans Regional Hospital, Hepato-gastroenterology Unit, CHR Orleans La Source, Orleans, Fr.
SOURCE: Journal of Hepatology (2000), 32(6), 1003-1010
CODEN: JOHEEC; ISSN: 0168-8278
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background/Aim: The aim of this prospective study was to compare the response to alfa-interferon **treatment** of chronic hepatitis C in two groups of patients: coinfected with **human** immunodeficiency **virus** (**HIV**) (G **I**) or not (G II). Methods: One hundred and fifty-three patients with chronic hepatitis C had been enrolled in 30 French liver units or infectious diseases units between May 1992 and Jan. 1995 (G I: 76, G II: 77) to receive alfa-**2a interferon**: 3 MU thrice weekly for 6 mo. Results: One hundred and twenty-seven patients (G I: 63, G II: 64) fulfilled all criteria for anal. The two groups were comparable for all demog. data, while significantly more severe biol. and histol. (p=0.001) parameters attested to more serious hepatitis among HIV-HCV coinfected patients. HCV viremia was higher among HIV-coinfected patients (p=0.0169), while genotype repartition was identical among the two groups (more than 52% of genotype 1, more than 31% of genotype 3). ALT normalization was, resp., (G I/G II) obtained in 17.46%/26.56% (not significant) of patients at the end of treatment and in 11.11%/12.5% (not significant) of patients after 6 mo of follow-up. In a multivariate anal., GGT level before therapy (relative risk 2.1, confidence interval 1.1-5.8) and body surface area (relative risk 1.9, confidence interval 1.1-3.7) were the variables independently assocd. with the response to alfa-interferon treatment (higher GGT and more elevated body surface area were assocd. with a risk of non-response). Conclusion: In our study HIV infection did not affect the alfa-interferon treatment response of chronic hepatitis C, and response could be achieved among HIV-coinfected patients. Present therapeutic anti-HCV schedules need to be proposed to HIV-HCV coinfected patients before severe immunosuppression occurs. On the other hand, more severe biol. and histol. parameters were obsd. among HIV-HCV coinfected patients, which suggests a need to study whether HIV infection is assocd. with a worsening course of chronic hepatitis C.
REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 17 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:383573 HCAPLUS
DOCUMENT NUMBER: 133:316
TITLE: Efficacy and safety of combination therapy with interferon-.alpha.2b and ribavirin for chronic hepatitis C in HIV-infected patients
AUTHOR(S): Landau, Alain; Batisse, Dominique; Van Huyen, Jean Paul Duong; Piketty, Christophe; Bloch, Francis; Pialoux, Gilles; Belec, Laurent; Petite, Jean Pierre; Weiss, Laurence; Kazatchkine, Michel D.

CORPORATE SOURCE: Department of Hepatology and Gastroenterology, Hopital Broussais, Paris, 75674, Fr.
SOURCE: AIDS (London) (2000), 14(7), 839-844
CODEN: AIDSET; ISSN: 0269-9370
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objectives: To evaluate the efficacy and safety of a combination therapy of interferon-.alpha.2b (IFN) and ribavirin for the treatment of chronic hepatitis C in HIV-seropos. patients. Design: Open prospective trial. Methods: Twenty patients co-infected with hepatitis C virus (HCV) and HIV, with a mean CD4 cell count of 350.+-.153 .times. 106/l were treated with IFN (3 MU three times per wk) in combination with ribavirin (500 mg or 600 mg twice a day) for 6 mo. Tolerance and efficacy were monitored at weeks 12 (month 3) and 24 (month 6). The primary endpoint was a complete virol. response, as defined by the lack of detectable HCV RNA in serum. Results: Baseline values of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were 121.+-.72 IU/l and 75.+-.67 IU/l, resp. The total Knodell score was 10.4.+-.2.4, with nine patients showing histol. evidence of active cirrhosis (45%). All patients exhibited circulating HCV RNA. The treatment was well tolerated, with no impact on the course of HIV infection. After 6 mo of combination therapy with IFN and ribavirin, 10 patients (50%) exhibited no further detectable HCV RNA viremia, seven of whom achieved undetectable viremia at month 3. Levels of ALT and AST decreased after 6 mo of treatment from a mean of 121.+-.72 to 51.+-.40 IU/l and from a mean of 129.+-.58 IU/l to 68.+-.61 IU/l, resp. ($P < 0.0002$ and $P < 0.0001$). Conclusion: Our results indicate that combination therapy with IFN and ribavirin is effective in 50% of cases in clearing serum HCV RNA and may thus provide effective means of therapy in HIV-HCV-coinfected patients as initial treatment or in patients who have previously failed IFN monotherapy.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 18 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:262806 HCAPLUS
DOCUMENT NUMBER: 132:274023
TITLE: HIV-related non-Hodgkin's lymphoma: CHOP induction therapy and interferon-.alpha.-2b/zidovudine maintenance therapy
AUTHOR(S): Weiss, Rudolf; Huhn, Dieter; Mitrou, Paris; Nerl, Christoph; Schurmann, Dirk; Scheidegger, Clemens; Knauf, Wolfgang; Trenn, Guido; Kronawitter, Ursula; Van Lunzen, Jan; Arasteh, Keikawus; Herbst, Hermann
CORPORATE SOURCE: Stadtische Kliniken Offenbach, Germany
SOURCE: Leukemia & Lymphoma (1998), 29(1/2), 103-118
CODEN: LELYEA; ISSN: 1042-8194
PUBLISHER: Harwood Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In a prospective multicenter study 68 out of 158 patients with HIV infection and malignant lymphoma were assigned to a risk-adapted induction therapy using the following algorithm: High-risk patients fulfilled 2 of 3 criteria: T4 lymphocytes <50/.mu.L; WHO activity

index 3 or 4; pre-existing AIDS-defining opportunistic infection. Normal-risk patients received 4 to 6 cycles of CHOP chemotherapy; those that achieved complete remission (CR) received zidovudine (500 mg/d) and interferon-.alpha. maintenance therapy (5 million units three times a week) for one year. High-risk patients received low-dose CHOP or vincristine/prednisone chemotherapy. Supportive care was performed with pentamidine inhalation and G-CSF. Intrathecal (it) methotrexate was given for CNS prophylaxis. The median survival was 634 days for 38 patients of the normal-risk group and 129 days for 30 patients of the high-risk group. 18 High-risk patients treated with low-dose CHOP had better survival (156 days) than 12 patients treated with vincristine/prednisone (72 days p = 0.044). 68% Of the patients in the normal-risk group achieved complete remission. 5 Out of 18 high-risk patients treated with low-dose CHOP achieved complete remission. Three normal-risk patients developed fatal opportunistic infections during chemotherapy. Immune parameters deteriorated after CHOP induction and partially recovered with maintenance treatment. We conclude that the normal-risk patients survived longer than reported in most published studies. Toxicity was low. Low-dose CHOP seems to be superior to vincristine/prednisone therapy in high-risk patients.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 19 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:353437 HCAPLUS
DOCUMENT NUMBER: 131:13242
TITLE: Activity of combination therapy with interferon alfa-2b plus ribavirin in chronic hepatitis C patients co-infected with HIV
AUTHOR(S): Dieterich, Douglas T.; Purow, Joshua M.; Rajapaksa, Roshini
CORPORATE SOURCE: Liberty Medical L.L.P., New York, NY, 10016, USA
SOURCE: Seminars in Liver Disease (1999), 19(Suppl. 1), 87-94
CODEN: SLDIEE; ISSN: 0272-8087
PUBLISHER: Thieme Medical Publishers, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 63 refs. The hepatitis C virus (HCV) and the human immunodeficiency virus (HIV) often co-infect the same individuals because they share comparable routes of transmission. Co-infection with HIV in those patients infected with HCV influences the accuracy of HCV diagnostic testing, levels of HCV viremia, severity of liver histopathol., and rate of progression to cirrhosis. By contrast, the effect of HCV co-infection on HIV disease is unclear. Nevertheless, the combination therapy contg. recombinant interferon alfa-2b (rIFN-.alpha.2b) plus ribavirin has been shown to be efficacious in the treatment of chronic hepatitis C, whereas alpha interferon monotherapy has been shown to be efficacious in patients co-infected with HCV and HIV. It is therefore logical to propose and test the hypothesis that combination rIFN-.alpha.2b/ribavirin therapy will also benefit patients who are co-infected with HCV and HIV. A double-blind, placebo-controlled study is presently under way to investigate this hypothesis.

REFERENCE COUNT: 63 THERE ARE 63 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE

IN THE RE FORMAT

L3 ANSWER 20 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:208505 HCAPLUS
DOCUMENT NUMBER: 130:276291
TITLE: Phase II, randomized, open-label, community-based trial to compare the safety and activity of combination therapy with recombinant interferon-.alpha.2b and zidovudine versus zidovudine alone in patients with asymptomatic to mildly symptomatic HIV infection
AUTHOR(S): Krown, Susan E.; Aeppli, Dorothee; Balfour, Henry H. , Jr.
CORPORATE SOURCE: Clinical Immunology Service, Department of Medicine, Memorial Sloan-Kettering Cancer Center and Cornell University Medical College, New York, NY, 10021, USA
SOURCE: Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology (1999), 20(3), 245-254
CODEN: JDSRET; ISSN: 1077-9450
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Aim of this study was to compare, in a community-based therapeutic setting, the safety, tolerance, and efficacy of combination therapy with recombinant **interferon**-.alpha.**2b** (rIFN-.alpha.2b) and zidovudine (ZDV) to ZDV monotherapy. Design was open-label, two-armed, randomized study. Asymptomatic or minimally symptomatic HIV-infected adults without an **AIDS** -defining illness, a CD4 count of 200 to 500 cells/.mu.l, and .ltoreq.6 mo of prior ZDV **therapy** received ZDV 100 mg orally five times daily. Patients randomized to rIFN-.alpha.2b received 3 million IU s.c. three times weekly for 2 wk and 5 million IU three times weekly thereafter. The groups were compared with respect to adverse events (AEs), dosing modifications, treatment discontinuation, clin. endpoints and changes in CD4 count. A virol. substudy compared the treatments with respect to HIV viral load and development of ZDV resistance. Between Oct., 1991 and Jan., 1993, 139 patients were randomized to combination therapy and 117 to ZDV alone. Of AEs reported at any grade, fatigue, myalgias, and sweating occurred significantly more often with combination therapy ($p < .001$). Study subjects receiving combination therapy showed modest but significantly greater wt. loss ($p = .0001$), a significantly higher frequency of any abnormal lab. test result ($p = .002$), neutropenia ($p = .002$), and leukopenia ($p = .02$), and also required dosage redn. for hematol. toxicity significantly more often ($p < .05$) than those in the ZDV monotherapy arm. No statistically significant differences were found between the groups with respect to development of specific AIDS-defining events, overall event rate, time to events, or change in performance status or CD4+ counts, or percentages or development of ZDV resistance. Viral burden, reflected by serum p24 antigen and quant. peripheral blood mononuclear cell (PBMC) microcultures, was greater at baseline in the combination therapy group. Baseline SI phenotype predicted progression to AIDS ($p = .004$, .CHI.2), whereas intermediate susceptibility to ZDV predicted development of ZDV resistance ($p < .005$, .CHI.2). The annual rate of development of phenotypic resistance to ZDV was 16.8% and was not affected by administration

of rIFN-.alpha.2b.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 21 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:121340 HCAPLUS
DOCUMENT NUMBER: 130:261433
TITLE: Clinical pharmacokinetics of lamivudine
AUTHOR(S): Johnson, Mark A.; Moore, Katy H. P.; Yuen, Geoffrey J.; Bye, Alan; Pakes, Gary E.
CORPORATE SOURCE: Glaxo Wellcome Research and Development, Greenford, UK
SOURCE: Clinical Pharmacokinetics (1999), 36(1), 41-66
CODEN: CPKNDH; ISSN: 0312-5963
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lamivudine (3TC), the neg. enantiomer of 2'-deoxy-3'-thiacytidine, is a dideoxynucleoside analog used in combination with other agents in the **treatment** of **human** immunodeficiency **virus** type **1** (**HIV-1**) infection and as monotherapy in the **treatment** of hepatitis B virus (HBV) infection. Lamivudine undergoes anabolic phosphorylation by intracellular kinases to form lamivudine 5'-triphosphate, the active anabolite which prevents HIV-1 and HBV replication by competitively inhibiting viral reverse transcriptase and terminating proviral DNA chain extension. The pharmacokinetics of lamivudine are similar in patients with HIV-1 or HBV infection, and healthy volunteers. The drug is rapidly absorbed after oral administration, with max. serum concns. usually attained 0.5 to 1.5 h after the dose. The abs. bioavailability is approx. 82 and 68% in adults and children, resp. Lamivudine systemic exposure, as measured by the area under the serum drug concn.-time curve (AUC), is not altered when it is administered with food. Lamivudine is widely distributed into total body fluid, the mean apparent vol. of distribution (Vd) being approx. 1.3 L/kg following i.v. administration. In pregnant women, lamivudine concns. in maternal serum, amniotic fluid, umbilical cord and neonatal serum are comparable, indicating that the drug diffuses freely across the placenta. In postpartum women lamivudine is secreted into breast milk. The concn. of lamivudine in cerebrospinal fluid (CSF) is low to modest, being 4 to 8% of serum concns. in adults and 9 to 17% of serum concns. in children measured at 2 to 4 h after the dose. In patients with normal renal function, about 5% of the parent compd. is metabolized to the trans-sulfoxide metabolite, which is pharmacol. inactive. In patients with renal impairment, the amt. of trans-sulfoxide metabolite recovered in the urine increases, presumably as a function of the decreased lamivudine elimination. As approx. 70% of an oral dose is eliminated renally as unchanged drug, the dose needs to be reduced in patients with renal insufficiency. Hepatic impairment does not affect the pharmacokinetics of lamivudine. Systemic clearance following single i.v. doses avs. 20 to 25 L/h (approx. 0.3 L/h/kg). The dominant elimination half-life of lamivudine is approx. 5 to 7 h, and the in vitro intracellular half-life of its active 5'-triphosphate anabolite is 10.5 to 15.5 h and 17 to 19 h in HIV-1 and HBV cell lines, resp. Drug interaction studies have shown that trimethoprim increases the AUC and decreases the renal clearance of

lamivudine, although lamivudine does not affect the disposition of trimethoprim. Other studies have demonstrated no significant interaction between lamivudine and zidovudine or between lamivudine and **interferon**-.alpha.-**2b**. There is limited potential for drug-drug interactions with compds. that are metabolized and/or highly protein bound.

REFERENCE COUNT: 70 THERE ARE 70 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 22 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:118424 HCAPLUS
DOCUMENT NUMBER: 130:236306
TITLE: Low dose oral interferon alpha 2a in HIV-1 seropositive patients: a double-blind, placebo-controlled trial
AUTHOR(S): Wright, Stephen E.; Hutcheson, David P.; Cummins, Joseph M.
CORPORATE SOURCE: Veterans Affairs Medical Center and Departments of Internal Medicine and Cell Biology & Biochemistry, Texas Tech University Health Sciences Center, Amarillo, TX, USA
SOURCE: Biotherapy (Dordrecht, Netherlands) (1998), 11(4), 229-234
CODEN: BTHREW; ISSN: 0921-299X
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Low dose oral interferon alpha has been shown to be of benefit in viral disease in animals. In a double-blind, placebo-controlled trial, 177 patients seropos. for HIV-1 were randomly assigned to receive placebo or recombinant human interferon alpha 2a (rIFN.alpha.). Endpoints were survival, alteration of disease classification, performance, and changes in CD4+ T cell nos. There was a trend for improved survival in the group receiving rIFN.alpha. at the dose of 1.0 IU/lb. The changes in disease classification or in wt. were not significantly different. Performance was improved to a greater extent (p=0.1) in the patients who received the two higher rIFN.alpha. dosages (1.0 IU/lb and 10.0 IU/lb) at 6 mo. In addn., the CD4+ T cell count was improved only in the 1.0 IU/lb dose treatment group at 6 mo. Treatment with low dose oral interferon at 1.0 IU/lb was assocd. with improved CD4+ T cell count, performance and a trend toward enhanced survival in HIV seropos. patients. These differences were, however, not statistically significant. A larger study, with better return rate, will be needed to det. whether low dose, oral interferon alpha is actually beneficial for these patients.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 23 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:681214 HCAPLUS
DOCUMENT NUMBER: 130:80163
TITLE: Treatment of chronic hepatitis D with interferon alpha-2b in patients with human immunodeficiency virus infection
AUTHOR(S): Puoti, Massimo; Rossi, Stefania; Forleo, Maria

Antonia; Zaltron, Serena; Spinetti, Angiola; Putzolu, Valeria; Rodella, Anna; Carosi, Giampiero
CORPORATE SOURCE: Department of Infectious Diseases, University of Brescia, Brescia, Italy
SOURCE: Journal of Hepatology (1998), 29(1), 45-52
CODEN: JOHEEC; ISSN: 0168-8278
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hepatitis delta virus (HDV) coinfection is frequent in patients infected with human immunodeficiency virus (HIV), and it may cause death independently of the development of full-blown AIDS. In order to evaluate the efficacy and tolerability of interferon alpha in the treatment of hepatitis delta in HIV-infected patients, and to compare them with those obsd. in anti-HIV-seroneg. patients, we carried out an open uncontrolled trial on 21 HIV-uninfected and 16 HIV-infected patients without severe immunodeficiency. All patients were treated with recombinant interferon alpha 2b (IFN) at doses of 10 million units thrice weekly for 6 mo, and 6 million units thrice weekly for an addnl. 6 mo. Patients showing alanine transaminase activity values persistently reduced by at least 50% from basal values received an addnl. 1-yr course of 3 million units thrice weekly. Alanine aminotransferase normalization was obsd. in 19% of HIV-infected and 14% of HIV-uninfected subjects during the first year; in 12% of HIV-infected and in 9% of HIV-uninfected patients during the second year. Twenty-five percent of HIV-infected and 14% of HIV-uninfected patients stopped IFN because of poor compliance or side effects. Two years after stopping interferon treatment, one anti-HIV-seropos. and two anti-HIV-seroneg. patients showed complete persistent biochem., virol. and histol. remission. Long-term efficacy and toxicity of IFN treatment seem not to be different in HIV-infected and -uninfected patients with delta hepatitis; given the overall poor rate of long-term response, IFN treatment could be considered only in immunocompetent HIV-HDV-coinfected patients, strictly selected because of rapidly evolving liver disease.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 24 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:146111 HCAPLUS
DOCUMENT NUMBER: 128:242668
TITLE: Safety profile of interferon-.alpha. therapy
AUTHOR(S): Weiss, Karen
CORPORATE SOURCE: Division of Clinical Trials Design and Analysis, Food and Drug Administration, Rockville, MD, 20892, USA
SOURCE: Seminars in Oncology (1998), 25(1, Suppl. 1), 9-13
CODEN: SOLGAV; ISSN: 0093-7754
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 11 refs. Two forms of recombinant **interferon** -.alpha. (**IFN**-.alpha.**2a** and **IFN** -.alpha.**2b**) have been approved by the Food and Drug Administration for a variety of clin. indications, including hairy

cell leukemia, hepatitis, **acquired** immunodeficiency **syndrome**-related Kaposi's sarcoma, chronic myelogenous leukemia (**IFN**-.alpha.**2a** only), and adjuvant **therapy** for melanoma (**IFN**-.alpha.**2b** only), based on their proven clin. efficacy and acceptable safety profiles. The continued postmarketing monitoring of adverse reactions assocd. with IFN-.alpha. therapy has revealed some new toxicities. The most common adverse events assocd. with IFN-.alpha. therapy are flu-like symptoms, fatigue, anorexia, and central nervous system and psychiatric reactions. In particular, the incidence of depression has only recently been fully appreciated. Some of these side effects, particularly chronic fatigue, anorexia, and neuropsychiatric reactions, may become dose limiting. New approaches to minimize and manage the side effects of IFN-.alpha. therapy are needed.

L3 ANSWER 25 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:5170 HCAPLUS
DOCUMENT NUMBER: 128:136118
TITLE: Safety and antiviral activity of combination **therapy** with zidovudine, zalcitabine, and two doses of **interferon**-.alpha. **2a** in patients with HIV: **AIDS** clinical trials group study 197
AUTHOR(S): Fischl, Margaret A.; Richman, Douglas D.; Saag, Michael; Meng, Tze Chiang; Squires, Kathleen E.; Holden-Wiltse, Jeanne; Meehan, Patricia M.
CORPORATE SOURCE: Department of Medicine, University of Miami School of Medicine, Miami, FL, 33101, USA
SOURCE: Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology (1997), 16(4), 247-253
CODEN: JDSRET; ISSN: 1077-9450
PUBLISHER: Lippincott-Raven Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We conducted a three-arm, randomized, phase II study to evaluate the combination of zidovudine (600 mg/day) and zalcitabine (2.25 mg/day) alone or with one of two **interferon**-.alpha.**2a** doses (1 mIU or 6 mIU daily). Primary study endpoints included toxicity and changes from baseline for plasma HIV-1 RNA, CD4 cells, and quant. microculture at weeks 8 and 24. Sixty-three patients with HIV infection and <400 CD4 cells/mm3 were enrolled; four patients discontinued therapy within 2 wk. Adverse event rates were 37%, 32%, and 60%, resp., for the nucleoside, 1-mIU interferon, and 6-mIU interferon combination groups. Increasing doses of interferon resulted in significantly greater hematol. toxicity ($p = 0.03$) and peripheral neuropathy ($p = 0.02$). Plasma **HIV-1** RNA redns. were noted across all **treatment** groups at week 8 ($p < 0.001$) but only for the nucleoside and 1-mIU interferon combination groups at week 24 ($p < 0.001$). Mean redns. in HIV-1 RNA at week 8 were 0.94, 1.29, and 1.40 log10, resp., for the nucleoside, 1-mIU interferon, and 6-mIU interferon combination groups ($p = 0.05$); no differences were noted at week 24. No differences in CD4 cell counts were seen. The addn. of **interferon**-.alpha.**2a** to zidovudine and zalcitabine resulted in transient enhanced decreases in viral load and increased toxicity.

L3 ANSWER 26 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:738791 HCAPLUS
DOCUMENT NUMBER: 128:60534
TITLE: Long-term treatment with recombinant interferon alpha-2b prolongs survival of asymptomatic HIV-infected individuals
AUTHOR(S): Rivero, J.; Fraga, M.; Cancio, I.; Cuervo, J.; Lopez-Saura, P.
CORPORATE SOURCE: Sanatorio "Santiago de las Vegas", Havana, Cuba
SOURCE: Biotherapy (Dordrecht, Netherlands) (1997), 10(2), 107-113
CODEN: BTHREW; ISSN: 0921-299X
PUBLISHER: Kluwer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Early long-term treatment with recombinant **interferon** (**IFN**) alpha-**2b** delayed disease progression in asymptomatic Human Immunodeficiency Virus (HIV) carriers in a randomized trial that lasted from Oct. 1987 to Feb. 1992 (14). The aim of the work reported in this paper was to observe if there was also an effect on survival when the same patients were followed-up further. **IFN** alpha-**2b** was given 3 .times. 106 IU, 3 times weekly. The control group did not receive any treatment. The main end-point for this evaluation was death due to any cause. The deadline was August 1995. Subjects were anti-HIV-1 seropos., Western blot-confirmed, asymptomatic (CDC group II), or with generalized lymphadenopathies (CDC group III). The groups had 79 (control) and 83 (IFN) patients. Mean survival was longer in the IFN group (95% CI: 127-152 vs. 101-120 mo since infection or 80-90 vs. 70-82 mo since the start of treatment). Survival rates were higher in IFN-treated individuals (61-77% vs. 24-54% at 10 yr of infection or 53-69% vs. 34-52% at 7 yr of treatment or follow-up). It was also confirmed that disease progression is significantly slower in IFN-treated patients. There were 23.4 vs. 3.2% long-term survivors in the IFN and control groups, resp. (p = 0.005). IFN-**treated** patients had fewer **AIDS**-related malignancies (5 vs. 11), mainly Kaposi's sarcomas (1 vs. 5). This difference was not statistically significant, but clin. interesting. There was no difference in survival if measured since the onset of AIDS. IFN alpha **treatment** given from the early stages of infection, but not after the appearance of **AIDS** symptoms, can prolong survival.

L3 ANSWER 27 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:698957 HCAPLUS
DOCUMENT NUMBER: 128:2771
TITLE: Interferon-.alpha. neutralizing antibodies in HIV and chronic HCV patients treated with natural-source human leukocyte-derived interferon-.alpha.n3
AUTHOR(S): Zhao, Xiao-Xia; Hua, Ji; Smith, Teresa; Ferencz-Biro, Katalin; Liao, Mei-June; Rashidbaigi, Abbas
CORPORATE SOURCE: Interferon Sciences, New Brunswick, NJ, 08901-3605, USA
SOURCE: Human Antibodies (1997), 8(3), 129-136
CODEN: HUANFP; ISSN: 1093-2607
PUBLISHER: Forefront Publishing

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Human leukocyte-derived IFN-.alpha.n3 (Alferon N Injection) was administered s.c. to **treat** 20 patients with asymptomatic **human** immunodeficiency **virus** type **1** (**HIV-1**) and 141 patients with chronic hepatitis C virus (HCV) infections. The **treatment** of **HIV-1** and HCV patients, previously untreated with any IFN prepns., did not result in development of neutralizing antibodies to IFN-.alpha.n3. Among 69 HCV refractory patients who were unresponsive to previous treatment with rIFN-.alpha.2b, 2 had neutralizing antibodies to rIFN-.alpha.**2b** prior to **IFN**-.alpha.n3 therapy, with no or limited cross-reactivity to IFN-.alpha.n3. After retreatment with IFN-.alpha.n3, both patients had detectable neutralizing titers to IFN-.alpha.n3. Addnl., 2 other patients developed low and transient neutralizing titers to IFN-.alpha.n3. Interferon subtype specificity of these antibodies was tested against RP-HPLC purified fractions of IFN-.alpha.n3, as well as rIFN-.alpha.2b and rIFN-.alpha.8b. Sera from patients previously treated with rIFN-.alpha.2b with high antibody titers to rIFN-.alpha.2b strongly reacted with the natural **IFN**-.alpha.**2b**, and to a limited extent with other IFN-.alpha. subtypes. Neutralizing activity against **IFN** -.alpha.**2b** was significantly competed out by the presence of a small amt. of other interferon subtypes present in IFN-.alpha.n3. One patient with prior presence of antibodies to **IFN**-.alpha.**2b** developed a high antibody titer to IFN-.alpha.8b with limited reactivity to IFN-.alpha.n3. Two of the HCV refractory patients with prior neutralizing antibodies to rIFN-.alpha.**2b** responded to **IFN**-.alpha.n3 therapy. These data suggest that the presence of neutralizing antibodies to individual IFN-.alpha. species will not significantly diminish the biol. activity and the clin. efficacy of multi-species IFN-.alpha.n3.

L3 ANSWER 28 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:329427 HCAPLUS
DOCUMENT NUMBER: 127:32644
TITLE: A multicenter controlled, randomized, open trial of interferon .alpha.2b treatment of anti-human immunodeficiency virus-negative hemophilic patients with chronic hepatitis C
AUTHOR(S): Rumi, Maria Grazia; Santagostino, Elena; Morfini, M.; Gringeri, A.; Tagariello, G.; Chistolini, A.; Pontisso, Patrizia; Tagger, A.; Colombo, M.; Mannucci, P. M.
CORPORATE SOURCE: Hepatitis Study Group of Association of Italian Hemophilia Centers, Institute of Internal Medicine and Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, University of Milan, IRCCS Maggiore Hospital, Milan, 20122, Italy
SOURCE: Blood (1997), 89(10), 3529-3533
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English
AB There is limited information about the long-term efficacy of prolonged **therapy** (more than 6 mo) with interferon .alpha.

in hemophilic patients with chronic hepatitis C who are not coinfected with the **human** immunodeficiency **virus** (**HIV-1**). One hundred and seven hemophiliacs were randomly assigned to 3 million U of **interferon** .alpha.**2b** three times weekly for 12 mo or no therapy. The patients were followed up for at least 12 mo posttreatment. Response was assessed by both serial alanine aminotransferase (ALT) levels and hepatitis C virus (HCV)-RNA measured by reverse transcribed polymerase chain reaction (RT-PCR) method. Before treatment, serum levels of HCV-RNA were measured quant. by second-generation branched-DNA assay and the HCV genotype was detd. by RT-PCR. Serum HGV-RNA, a marker of infection with the hepatitis G virus, was also measured by RT-PCR. Normalization of AL was sustained and serum HCV-RNA was cleared in 6 of 45 treated patients, compared with none of the 50 untreated controls (13% v 0% P < 01). Low pretreatment viremia was the only feature that was assocd. with an increased likelihood of sustained response (P <.01). This study shows that multi-transfused hemophiliacs with chronic hepatitis C not coinfected with **HIV-1** respond at low rates to prolonged interferon **therapy**.

L3 ANSWER 29 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:258154 HCAPLUS
DOCUMENT NUMBER: 124:332120
TITLE: A phase II study of recombinant human interferon-.alpha.2a and zidovudine in patients with AIDS-related Kaposi's sarcoma
AUTHOR(S): Fischl, Margaret A.; Finkelstein, Dianne M.; He, Weili; Powderly, William G.; Triozzi, Pierre L.; Steigbigel, Roy T.
CORPORATE SOURCE: School Medicine, University Miami, Miami, FL, 33101, USA
SOURCE: Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology (1996), 11(4), 379-84
CODEN: JDSRET; ISSN: 1077-9450
PUBLISHER: Lippincott-Raven
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To assess safety, antitumor response, and immunol. and virol. activity of **interferon**-.alpha.**2a** and zidovudine combination **therapy** in patients with **AIDS** -related Kaposi's sarcoma, we conducted an open-label, Phase II, multicenter study. Sixty-three patients with biopsy-proven Kaposi's sarcoma and no previous interferon-.alpha. therapy received zidovudine 600 mg/day and **interferon**-.alpha.**2a** 18 .times. 106 U/day. The median duration of follow-up was 49 wk. Of 62 evaluable patients, 25 (40%; 95% confidence interval, 0.28-0.52) showed a complete (26%) or partial (15%) antitumor response. Eight of 30 patients (27%) with <100 CD4 cells/mm3 and 17 of 32 patients (53%) with .gtoreq.100 CD4 cells/mm3 had a response. The median time to response was 36 wk. Of the 25 patients with a response, four developed tumor progression. The median duration of response was 22.4 wk. Eight patients (13%) developed another AIDS-defining event and 13 (21%) died. The major toxicities included anemia (16%), neutropenia (27%), elevated serum transaminases (16%), wt. loss (16%), malaise (14%), fatigue (14%), fever (10%), and headache (6%). **Therapy** with intermediate-dose **interferon**-.alpha.**2a** and

zidovudine resulted in tumor regression in patients with **AIDS**-related Kaposi's sarcoma who had a wide range of CD4 cell counts; this **therapy** was relatively well tolerated.

L3 ANSWER 30 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:58293 HCAPLUS
DOCUMENT NUMBER: 124:76500
TITLE: Methods for the identification of compounds capable of abrogating HIV-1 vpr-rip-1 binding interactions, treatment methods, and pharmaceutical compositions
INVENTOR(S): Weiner, David B.; Refaeli, Yosef
PATENT ASSIGNEE(S): Trustees of the University of Pennsylvania, USA
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9531901	A1	19951130	WO 1995-US5981	19950517
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5639598	A	19970617	US 1994-246177	19940519
US 5780220	A	19980714	US 1995-382873	19950203
AU 9525880	A1	19951218	AU 1995-25880	19950511
AU 690694	B2	19980430		
EP 759693	A1	19970305	EP 1995-920426	19950517
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				

PRIORITY APPLN. INFO.:
US 1994-246177 19940519
US 1995-382873 19950203
WO 1995-US5981 19950517

AB A method for treating an individual exposed to or infected with HIV is disclosed which comprises administering to said individual a therapeutically effective amt. of one or more compds. which inhibit or prevent replication of said HIV by interfering with the replicative or other essential functions of vpr expressed by the HIV, by interactively blocking the vpr target in human cells, and thereby preventing translocation of the vpr/target complex from the cytosol of said human cells to the nuclei of said cells, where vpr carries on activities essential to replication of HIV. In preferred embodiments, the compd. or compds. which interactively block the target are steroid hormone receptor antagonists, glucocorticoid receptor antagonists, or glucocorticoid receptor Type II antagonists, esp. mifepristone (RU-486). Pharmaceutical compns. comprising these compds., as well as a method for identifying them and a kit for use therein, are also disclosed.

L3 ANSWER 31 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:679423 HCAPLUS

TITLE: Use of recombinant interferon-.alpha. in human immunodeficiency virus (HIV)-infected individuals
AUTHOR(S): Rivero, J.; Limonta, M.; Aguilera, A.; Fraga, M.; Lopez Saura, P.
CORPORATE SOURCE: Santiago de las Vegas Sanatorium, The Center for Genetic Engineering and Biotechnology, Havana, Cuba
SOURCE: Biotherapy (Dordrecht, Netherlands) (1995), Volume Date 1994, 8(1), 23-31
CODEN: BTHREW; ISSN: 0921-299X
PUBLISHER: Kluwer
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Rationale and objective: Interferon alpha (IFN-.alpha.) has anti-retroviral activity and is a possible HIV infection-limiting factor. The aim of this work is to prevent or delay disease progression in asymptomatic Human Immunodeficiency Virus (HIV) carriers. Design and interventions: Recombinant **IFN** alpha-**2b** (3 .times. 106 IU 3 times weekly) was compared, to no treatment (control) in a randomized trial. Endpoints were: (i) appearance of any CDC group IV symptoms and (ii) disease progression (which excluded shifts to group IVC2 or reversible IVA, or IVB). The trial lasted from Oct. 1987 to Feb. 1992. Setting: The trial was performed at the "Santiago de las Vegas" sanatorium, a specialized institution for the cate of HIV-infected and AIDS patients. Population: Subjects were anti-HIV-1 seropos., Western blot-confirmed, asymptomatic (CDC group II), or with generalized lymphadenopathies (CDC group III). The groups had 79 (control) and 71 (IFN) patients. Main results: Long-term IFN-.alpha. **treatments** significantly reduced the proportion of patients who shifted to any group IV (control: 46/79; IFN:14/71; $p < 0.001$) or developed **AIDS** (control: 27/79; IFN: 12/71; $p < 0.05$). IFN ALSO DELAYED PROGRESSION TO aids (95% confidence interval for 0.5 probability of progression) from 67-83 to 116-180 mo after infection. The IFN group had significantly less opportunistic infections and non-infectious complications. CD4 cell count and Hb decreased in the control but not in the IFN group. Fewer IFN-treated patients developed pos. serum HIV antigen detection. Conclusion: IFN alpha treatment during the early stages of infection seems to be beneficial to the patients. Abbreviations: CI: confidence interval, AIDS: Acquired Immunodeficiency syndrome, HIV: Human Immunodeficiency Virus, IFN: Interferon, CDC: Center for Disease Control (USA), SD; std. deviation.

L3 ANSWER 32 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1995:585191 HCAPLUS
TITLE: Anti-alpha interferon immunization: safety and immunogenicity in asymptomatic HIV positive patients at high risk of disease progression
AUTHOR(S): Gringeri, Alessandro; Santagostino, Elena; Mannucci, Pier Mannuccio; Siracusano, Licia; Marinoni, Alessandra; Criscuolo, Marcelo; Carcagno, Miguel; Fall, Lat-S.; M'Bika, Jean-Pierre; et al.
CORPORATE SOURCE: Inst. Internal Med., Univ. Milan, Milan, 20122, Italy
SOURCE: Cellular and Molecular Biology (Paris) (1995),

41(3), 381-7
CODEN: CMOBEF; ISSN: 0145-5680
PUBLISHER: C.M.B. Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A randomized, placebo-controlled trial was designated to evaluate safety and immunogenicity of an anti-cytokine vaccine in high risk HIV-pos. patients. This strategy was aimed to modulate the impaired cytokine regulation in AIDS. Twelve asymptomatic patients on antiretroviral therapy for at least 1 yr and with CD4 cell counts between 100-300/mm3 were randomized to receive adjuvanted formol-inactivated **interferon** alpha-**2a** (INF.alpha.) and continue t6he current antiretroviral treatment, whatever it was, or to receive the adjuvant alone and the current antiretroviral treatment. All patients received 4 i.m. injections monthly, followed by booster injections every 3 mo. Clin. status, immunol. and virol. were monitored. Immune response to vaccination was evaluated in term of antibody detection (ELISA) and serum anti-IFN.alpha. neutralizing capacity. Only local disconfort and transient fever were reported. All vaccinees except one showed increased levels of anti-IFN.alpha. Abs and developed serum IFN.alpha. neutralizing capacity. Viral load did not increase in vaccinees while it remained unchanged or even increased in placebo-treated patients. None of them showed HIV-related symptoms and all had their CD4 cell counts stabilized over 18 mo, whereas 2 placebo-**treated** patients developed full-blown **AIDS** . In conclusion, anti-IFN.alpha. vaccine was safe and immunogenic. Stable clin. and immunol. status over 18 mo was obsd. in vaccinees coupled to increased serum IFN.alpha. neutralizing capacity.

L3 ANSWER 33 OF 36 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:292427 HCAPLUS
DOCUMENT NUMBER: 122:122557
TITLE: Inhibition of human immunodeficiency virus type 1 replication in cytokine-stimulated monocytes/macrophages by combination therapy
AUTHOR(S): Rusconi, Stefano; Merrill, Debra P.; Hirsch, Martin S.
CORPORATE SOURCE: Harvard Medical School, Massachusetts General Hospital, Boston, MA, 02114, USA
SOURCE: Journal of Infectious Diseases (1994), 170(6), 1361-6
CODEN: JIDIAQ; ISSN: 0022-1899
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Combination regimens against human immunodeficiency virus type 1 (HIV-1) were studied in granulocyte-macrophage colony-stimulating factor (GM-CSF)-stimulated monocyte/macrophage cultures. Regimens included those that inhibited the same target (reverse transcriptase) or multiple targets. Treatment conditions assessed efficacy during prophylaxis and ongoing infection. Drugs included zidovudine, didanosine, nevirapine, foscarnet, pyridinone, the protease inhibitor RO31-8959 (also known as saquinavir), interferon-.alpha.A, the Tat inhibitor RO24-7429, and N-butyl-deoxynojirimycin. Two-, three-, and four-drug combinations were tested. Drugs were tested at individually inhibitory concns. of IC99, IC95, IC75, and IC50. All prophylactic regimens prevented HIV-1 replication at IC99. As drug concns. were reduced,

differences among the regimens became apparent. Regiments that acted at both single and multiple targets were effective in prophylactic settings and less so in acute infection. In ongoing infections, only modest redns. in viral replication were seen, even at IC99.

L3 ANSWER 34 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:215148 HCAPLUS
DOCUMENT NUMBER: 120:215148
TITLE: Increased efficacy of human natural interferon .alpha. (IFN-.alpha.n3) versus human recombinant IFN-.alpha.2 for inhibition of HIV-1 replication in primary human monocytes
AUTHOR(S): Fan, Sharon X.; Skillman, Donald R.; Liao, Mei June; Testa, Douglas; Meltzer, Monte S.
CORPORATE SOURCE: Dep. Cell. Immunol., Walter Reed Army Inst. Res., Washington, DC, 20307-5100, USA
SOURCE: AIDS Research and Human Retroviruses (1993), 9(11), 1115-22
CODEN: ARHRE7; ISSN: 0889-2229
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Natural IFN-.alpha.n3, a purified mixt. of many different natural IFN.alpha. species, was 10-100-fold more effective than equal concns. of human rIFN-.alpha.2b or rIFN-.alpha.2a for inhibition of HIV replication in primary human monocytes. This difference was highly reproducible in multiple side-by-side expts. using the identical **HIV-1** inoculum and the same monocyte target cells: natural IFN-.alpha.n3 was more effective than rIFN-.alpha.2b at lower concns. for protection against a const. **HIV-1** inoculum; cells **treated** with natural IFN-.alpha.n3 were protected against a greater **HIV -1** challenge than were cells **treated** with the same concn. of rIFN-.alpha.2b. Fractionation of natural IFN-.alpha.n3 by reversed-phase high-pressure liq. chromatog. (RP-HPLC) showed that most antiviral activity for HIV localized to discrete and reproducible peaks. The RP-HPLC peak that contained purified natural **IFN**-.alpha.**2b** was the least effective fraction. These data suggest heterogeneity among IFN-.alpha. species for antiviral activity against HIV and may provide a mol. basis for more effective IFN-.alpha. therapy.

L3 ANSWER 35 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1990:570159 HCAPLUS
DOCUMENT NUMBER: 113:170159
TITLE: Alpha interferon (2b) in combination with zidovudine for the treatment of presymptomatic feline leukemia virus-induced immunodeficiency syndrome
AUTHOR(S): Zeidner, Nordin S.; Myles, Matthew H.; Mathiason-DuBard, Candace K.; Dreitz, Matthew J.; Mullins, James I.; Hoover, Edward A.
CORPORATE SOURCE: Dep. Pathol., Colorado State Univ., Fort Collins, CO, 80523, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1990), 34(9), 1749-56
CODEN: AMACCQ; ISSN: 0066-4804
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The **therapeutic** efficacies of human recombinant alpha interferon (IFN-.alpha.), IFN-.alpha. plus zidovudine (AZT), and AZT alone were evaluated in presymptomatic cats with established feline leukemia virus (FeLV)-**acquired** immunodeficiency **syndrome** (FAIDS) infection and high levels of persistent antigenemia. S.c. injection of 1.6 x 106 U of human recombinant **IFN-**.alpha. **2b** per kg delivered peak concns. in plasma of 3,600 U/mL at 2 h postadministration with a half-life of elimination of 2.9 h. This dosage of IFN-.alpha. could be delivered to cats for up to 12 wk without significant clin. toxicity. Oral administration of AZT (20 mg/kg three times daily) resulted in peak concns. in plasma of 3 .mu.g/mL at 2 h with a half-life of elimination of approx. 1.60 h. Treatment of FeLV-FAIDS-infected cats with IFN-.alpha., either alone or in combination with orally administered AZT, resulted in decreases in circulating p27 core antigen beginning 2 wk after the initiation of therapy. AZT alone had no effect on circulating virus antigen. Depending upon whether high (1.6 x 106 U/kg) or low (1.6 x 104 to 1.6 x 105 U/kg)-dosage IFN-.alpha. was used, cats became refractory to therapy 3 or 7 wk after the beginning of treatment. At these times, IFN-.alpha.-treated animals developed antibodies to IFN-.alpha. that were neutralizing, specific for human recombinant IFN-.alpha., and dose dependent in magnitude. The results of this study indicate that human recombinant IFN-.alpha. is effective in reducing circulating virus antigenic load in cats persistently infected with FeLV-FAIDS. However, the continued efficacy of IFN-.alpha. therapy appeared to be limited by the formation of cytokine-specific neutralizing antibodies.

L3 ANSWER 36 OF 36 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1989:210820 HCAPLUS
DOCUMENT NUMBER: 110:210820
TITLE: **Treatment** of **AIDS** virus infection with recombinant human .alpha. **interferon** .alpha.-**2b**
INVENTOR(S): Feinberg, Judith
PATENT ASSIGNEE(S): Schering Corp., USA
SOURCE: Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 266940	A1	19880511	EP 1987-309312	19871021
EP 266940	B1	19921216		
R: AT, BE, CH, DE, ES, FR, GB, GR, IT, LI, LU, NL, SE				
CA 1297788	A1	19920324	CA 1987-549813	19871021
AT 83381	E	19930115	AT 1987-309312	19871021
ES 2052579	T3	19940716	ES 1987-309312	19871021
JP 63104929	A2	19880510	JP 1987-267607	19871022
PRIORITY APPLN. INFO.:			US 1986-921922	19861022
			EP 1987-309312	19871021

AB Patients infected with **AIDS** virus are rendered aviremic by **treatment** with high doses of recombinant human

.alpha.-interferon (no data). Procedures for a randomized, double-blind, placebo-controlled study on AIDS virus-seropos. patients are described. Treated patients received 35 .times. 106 IU human recombinant .alpha.**2b-interferon**/day for .gtoreq.12 wk.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 09:12:35 ON 13 JUN 2003)

L4 214 S L3
L5 39 S L4(L)ADMIN?
L6 22 DUP REM L5 (17 DUPLICATES REMOVED)

L6 ANSWER 1 OF 22 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2003105402 EMBASE
TITLE: Perforin expression in T cells and virological response to PEG-interferon alpha2b in HIV-1, infection.
AUTHOR: Portales P.; Reynes J.; Rouzier-Panis R.; Baillat V.; Clot J.; Corbeau P.
CORPORATE SOURCE: P. Corbeau, Laboratoire d'Immunologie, Hopital Saint Eloi, 80 avenue A. Fliche, 34.295, Montpellier Cedex 5, France. pierre.corbeau@igh.cnrs.fr
SOURCE: AIDS, (7 Mar 2003) 17/4 (505-511).
Refs: 28
ISSN: 0269-9370 CODEN: AIDSET
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Objective and design: Interferon .alpha. (IFN.alpha.) which is known to directly inhibit the **HIV-1** replicative cycle and to increase the activity of cytotoxic T lymphocytes (CTL), is being tested as an anti-HIV agent. As CTL play a major role in immune defence against HIV, we wanted to further characterize CTL activity and the effect of IFN.alpha. on it. Methods: We followed by flow cytometry the intracellular expression of the key mediator of cytotoxicity, perforin, in peripheral blood T cells of patients **treated** with IFN.alpha.. Results: We observed that the percentage of T cells harbouring perforin was higher in infected subjects than in non-infected controls. **Administration** of **IFN**.alpha.**2b** attached to polyethylene glycol increased this perforin expression further and reduced viral load (P = 0.010). The increase in the percentage of T cells expressing perforin correlated with IFN.alpha.-induced decrease in viral load (r, 0.753; P = 0.003). In addition, the level of perforin expression before IFN.alpha. **administration** was inversely correlated with viral load remaining after IFN.alpha. **administration** (r, -0.647; P = 0.017). Conclusion: The pre-**therapeutic** percentage of perforin-positive T'cells might be a predictive marker of the virological response to IFN.alpha. in **HIV-1** -infected patients. .COPYRGT. 2003 Lippincott Williams & Wilkins.

L6 ANSWER 2 OF 22 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2003-058392 [05] WPIDS

DOC. NO. CPI: C2003-014887
TITLE: Composition useful for treatment of AIDS, bacterial infection, fungal infection, parasitic infection and chronic viral infection e.g. hepatitis B and C, HIV, comprises aerosolized interleukin-2 liposomes.
DERWENT CLASS: B04 B07
INVENTOR(S): ANDERSON, P M; ZEIN, N N
PATENT ASSIGNEE(S): (MAYO-N) MAYO FOUND MEDICAL EDUCATION RES
COUNTRY COUNT: 100
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002078624	A2	20021010	(200305)*	EN	30

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002078624	A2	WO 2002-US9129	20020326

PRIORITY APPLN. INFO: US 2001-280209P 20010330
AN 2003-058392 [05] WPIDS
AB WO 200278624 A UPAB: 20030121
NOVELTY - A composition comprises interleukin-2 (IL-2) liposomes.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) Treatment of a chronic viral infection involves **administering** IL-2 liposome;
(2) A kit comprising sterile, lyophilized IL-2 liposome; and
(3) An inhaler or nebulizer comprising the composition.
ACTIVITY - Hepatotropic; Antiinflammatory; Anti-HIV; Virucide; Fungicide; Antiparasitic; Antibacterial; Immunostimulant.
MECHANISM OF ACTION - Viral growth inhibitor.
USE - For **treating** a chronic viral infection e.g. hepatitis B and C, HIV, and **AIDS**, bacterial infection, other viral infections, fungal infection, parasitic infection, and immunodeficiency condition e.g. common variable immunodeficiency (claimed).
Twenty nine patients with serologic, virologic, and histologic evidences of hepatitis C virus (HCV) were given a triple therapy with aerosol interleukin-2 (IL-2) liposomes plus **interferon** alpha **-2b**/ribavirin (**IFN**/R) for 24 weeks. The dose given was 1 MU of aerosol IL-2 liposomes twice daily every other week. Sixteen of 29 patients have completed therapy. Five of 16 had sustained virologic and biochemical responses. Three patients who had a repeat liver biopsy after discontinuation of treatment had point decline in fibrosis stage. Two of 3 patents with improved fibrosis stage had no sustained virologic response to triple therapy. No serious adverse events associated with the triple

therapy were observed. All patients demonstrated 10 fold decrease in viral RNA titer. Some patients had elimination of detectable virus and other even had reduction in cirrhosis on liver biopsy.

ADVANTAGE - The chronic self-**administration** of aerosol IL-2 liposome is feasible in patients with chronic hepatitis C; has excellent patient acceptance; low toxicity; and is effective in decreasing viral titers and viral loads.

Dwg.0/3

L6 ANSWER 3 OF 22 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2003-361778 [34] WPIDS
DOC. NO. CPI: C2003-095410
TITLE: Treatment of patients having human immunodefficiency virus infections, comprises administering pegylated interferon-alfa to lower detectable human immunodefficiency virus-ribonucleic acid.
DERWENT CLASS: B04
INVENTOR(S): GLUE, P W; LAUGHLIN, M A; STALGIS, C O
PATENT ASSIGNEE(S): (GLUE-I) GLUE P W; (LAUG-I) LAUGHLIN M A; (STAL-I) STALGIS C O
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002182179	A1	20021205	(200334)*		14

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002182179	A1	Provisional US 1999-122370P	19990302
		Provisional US 1999-124304P	19990312
		Provisional US 1999-128296P	19990408
		US 2000-516673	20000301

PRIORITY APPLN. INFO: US 2000-516673 20000301; US 1999-122370P 19990302; US 1999-124304P 19990312; US 1999-128296P 19990408

AN 2003-361778 [34] WPIDS
AB US2002182179 A UPAB: 20030529

NOVELTY - **Treatment** of patients having **HIV-1** infections, comprises **administration** of an amount of pegylated interferon- alpha (**I**) to lower detectable **HIV-1**-RNA.

ACTIVITY - Anti-HIV; Virucide; Hepatotropic; Antiinflammatory.

Treatment naive or **treatment**-experienced male and female patients diagnosed with **HIV-1** infection were randomized to receive **interferon** alpha -**2b**, i.e. PEG12000-**interferon** alpha -**2b** at doses of 0.5, 1.0, 1.5, 3.0 and 4.5 mu g/kg by subcutaneous injection once a week. HAART was also initiated before or concurrently with the **administration** of the pegylated **interferon** alpha -**2b** (i.e., PEG-Intron (RTM)).

Plasma HIV-1-RNA/qPCR testing was conducted by Amplicator test, version 1.5 of greater than 500 copies/ml. The result showed a lower

HIV-I-RNA plasma levels by a factor of at least 0.5 log10.

MECHANISM OF ACTION - Nucleoside reverse transcriptase inhibitors (NRTI); Non-NRTI; HIV protease inhibitor.

USE - Method is used for **treating** patients, e.g. **treatment**-naive or **treatment**-experienced adult or pediatric patients, co-infected with **HIV-1** and HCV.

ADVANTAGE - The inventive method minimizes HIV-1-RNA plasma levels by, e.g. at least 0.5 multiply 10-1 (preferably at least 0.65 log10).

Dwg.0/0

L6 ANSWER 4 OF 22 WPIDS (C) 2003 THOMSON DERWENT

ACCESSION NUMBER: 2002-034430 [04] WPIDS
DOC. NO. CPI: C2002-009642
TITLE: New ribavirin derivatives, useful for treating viral infections, particularly chronic hepatitis C infection, optionally in combination with interferon alpha.
DERWENT CLASS: B02 B03
INVENTOR(S): BENNETT, F; GANGULY, A K; GIRIJAVALLABHAN, V M; LOVEY, R G; MCCORMICK, J; SAKSENA, A K
PATENT ASSIGNEE(S): (SCHE) SCHERING CORP; (BENN-I) BENNETT F; (GANG-I) GANGULY A K; (GIRI-I) GIRIJAVALLABHAN V M; (LOVE-I) LOVEY R G; (MCCO-I) MCCORMICK J; (SAKS-I) SAKSENA A K
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001081359	A1	20011101	(200204)*	EN	104
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CZ DE DK DM DZ EE ES FI GB GD GE HR HU ID IL IN IS JP KG KR KZ LC LK LR LT LU LV MA MD MG MK MN MX MZ NO NZ PL PT RO RU SE SG SI SK SL TJ TM TR TT TZ UA US UZ VN YU ZA					
AU 2001055495	A	20011107	(200219)		
US 2002055473	A1	20020509	(200235)		
EP 1282632	A1	20030212	(200312)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001081359	A1	WO 2001-US12760	20010418
AU 2001055495	A	AU 2001-55495	20010418
US 2002055473	A1 Provisional	US 2000-198801P	20000420
		US 2001-837491	20010418
EP 1282632	A1	EP 2001-928662	20010418
		WO 2001-US12760	20010418

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 2001055495 A Based on WO 200181359
EP 1282632 A1 Based on WO 200181359

PRIORITY APPLN. INFO: US 2000-198801P 20000420; US 2001-837491 20010418
AN 2002-034430 [04] WPIDS
AB WO 200181359 A UPAB: 20020117
NOVELTY - Ribavirin derivatives (I) and their salts are new.
DETAILED DESCRIPTION - Ribavirin derivatives of formula (I) and their salts are new.
at least 1 of R2, R3 and R5 = H, R20-(W)x-CO-, R20 (W)x-CS- or R20-(W)x-PO(OH)-; and at least 1 of R2, R3 and R5 is not H;
R20 = H; cycloalkyl; heterocyclic; NR21R22; alkyl, alkanoyl or alkenyl, alkynyl, each optionally substituted by Q; aryl optionally substituted by Q1; -(CHR21)e-(CH2)f-CO-OR22; -(CHR21)e-(CH2)f-OR22; or -(CHR21)e-(CH2)f NR21R22;
Q = halo, phenyl, cycloalkyl, NR21R22, OH or alkoxy;
Q1 = phenyl, halo, CN, NO2, OH, R28, OR28, CF3, SH, SR21, SOR21, SO2R21, NR21R22, CO2H, CO2-, OR21, O-M+ or S-M+;
M+ = an alkali metal cation;
W = O, NR28 or S;
R21 = H; or alkyl, alkanoyl or aryl, each optionally substituted by Q2;
R22 = H; or alkyl or aryl, each optionally substituted by Q2;
Q2 = halo, phenyl, CN, NO2, OH, CO2H or alkoxy;
or R21 and R22 together with N to which they are attached and 1 of CHR21, O, S, SO or SO2 form a 5-7 membered ring;
R27 = H, OR21, NR21R22, R20-(W)x-CO-, R20-(W)x-CS-, (HO)2PO-;R20-(W)x-PO(OH)- or HO-SO2-;
R28 = H; alkanoyl; aryl; or alkyl optionally substituted by OH, halo or NR21R22;
e = 0-6;
f = 0-10;
t = 0-100;
s = 0-6000;
r = 1-5000; and
x = 0-1.
INDEPENDENT CLAIMS are included for the use of (I), optionally in combination with interferon alpha, for treating a chronic hepatitis infection.
ACTIVITY - Virucide; Hepatotropic; Antiinflammmatory; Anti HIV.
MECHANISM OF ACTION - None given in the source material.
USE - (I) are useful for treating viral infections, particularly chronic hepatitis C infection in combination with interferon- alpha (preferably **interferon** alpha -**2a** or alpha -**2b**, a consensus **interferon**, a purified interferon- alpha product, a pegylated **interferon** alpha -**2a**, pegylated **interferon** alpha -**2b**, or pegylated consensus **interferon**) (claimed).
The combination **therapy** may also be **administered** in association with anti-retroviral **therapy**, to a patient co-infected with **HIV-1** and HCV.
Dwg.0/0

L6 ANSWER 5 OF 22 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 2001164782 EMBASE

TITLE: The combination of zidovudine and interferon alpha-2B in the treatment of adult T-cell leukemia/lymphoma.

AUTHOR: White J.D.; Wharfe G.; Stewart D.M.; Maher V.E.; Eicher D.; Herring B.; Derby M.; Jackson-Booth P.-G.; Marshall M.; Lucy D.; Jain A.; Cranston B.; Hanchard B.; Lee C.C.; Top L.E.; Fleisher T.A.; Nelson D.L.; Waldmann T.A.

CORPORATE SOURCE: Dr. J.D. White, National Cancer Institute, National Institutes of Health, Cancer Complement./Alternative Med., 6130 Executive Boulevard, Bethesda, MD 20892, United States

SOURCE: Leukemia and Lymphoma, (2001) 40/3-4 (287-294).
Refs: 34
ISSN: 1042-8194 CODEN: LELYEA

COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
025 Hematology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles

LANGUAGE: English
SUMMARY LANGUAGE: English

AB Adult T-cell leukemia/lymphoma (ATL) is frequently a very aggressive malignancy with a poor survival despite aggressive multiagent chemotherapy. The combination of the antiretroviral drug zidovudine (AZT) and interferon alpha (IFN.alpha.) has been reported to induce remissions in patients with ATL. The purpose of this study was to evaluate the clinical response and toxicity following **administration** of a combination of **IFN**.alpha.-**2b** and AZT in patients with **human** T-cell lymphotropic **virus** type **I** (**HTLV-I**)-associated ATL. Eighteen patients with ATL (chronic, crisis, acute or lymphoma type) were **treated** with the combination of AZT (50 - 200 mg orally 5 times a day) and **IFN**.alpha.-**2b** (2.5 - 10 million units subcutaneously daily). Three patients had objective responses lasting more than one month. One patient had a clinical complete remission, lasting 21.6 months and two patients had partial remissions lasting 3.7 and 26.5 months. Six patients were not considered evaluable for response due to short and/or interrupted periods of **treatment**. Seventeen patients have died with a median survival time after initiation of **therapy** of 6 months. Neutropenia and thrombocytopenia were the dose limiting toxicities. In conclusion, the response rate in this study was lower than noted in the two previous published series. This may be due to the amount and type of prior **treatment** our patients had received.

L6 ANSWER 6 OF 22 WPIDS (C) 2003 THOMSON DERWENT

ACCESSION NUMBER: 2000-587254 [55] WPIDS
DOC. NO. CPI: C2000-175086

TITLE: Use of a pegylated interferon-alpha for treating HIV-1 patients, especially those co-infected with hepatitis C.

DERWENT CLASS: A96 B04

INVENTOR(S): GLUE, P W; LAUGHLIN, M A; STALGIS, C O
PATENT ASSIGNEE(S): (SCHE) SCHERING CORP

COUNTRY COUNT: 89
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000051631	A2	20000908	(200055)*	EN	45
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CZ DE DK DM EE ES FI GB GD GE HR HU ID IL IN IS JP KG KR KZ LC LK LR LT LU LV MA MD MG MK MN MX NO NZ PL PT RO RU SE SG SI SK SL TJ TM TR TT TZ UA US UZ VN YU ZA					
EP 1034790	A2	20000913	(200055)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
CA 2299893	A1	20000902	(200059)	EN	
JP 2000256211	A	20000919	(200060)		18
AU 2000037148	A	20000921	(200065)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000051631	A2	WO 2000-US5361	20000301
EP 1034790	A2	EP 2000-301695	20000302
CA 2299893	A1	CA 2000-2299893	20000301
JP 2000256211	A	JP 2000-55695	20000301
AU 2000037148	A	AU 2000-37148	20000301

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000037148	A	Based on	WO 200051631

PRIORITY APPLN. INFO: US 1999-454004 19991203; US 1999-260388 19990302; US 1999-268521 19990312; US 1999-288358 19990408

AN 2000-587254 [55] WPIDS

AB WO 200051631 A UPAB: 20001102
NOVELTY - Use of a pegylated interferon-alpha for preparation of a medicament for treating human immuno-virus-1 (HIV-1) infections, is new.

(N.B. ''Pegylated interferon-alpha'' indicates polyethylene glycol modified conjugates of interferon-alpha).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for the use of an anti-HIV-1 drug therapy and pegylated interferon-alpha for the preparation of a medicament for treating HIV-1 infections.

ACTIVITY - Anti-HIV; Virucide; Hepatotropic
Tests are described but no results are given.

USE - The methods are for the treatment of adult and pediatric HIV-1 patients, especially those co-infected with HCV.

ADVANTAGE - The methods aim to lower detectable HIV-1 RNA in patients.

Dwg.0/0

L6 ANSWER 7 OF 22 WPIDS (C) 2003 THOMSON DERWENT

ACCESSION NUMBER: 2000-410878 [35] WPIDS
CROSS REFERENCE: 1997-470878 [43]; 2002-105276 [06]
DOC. NO. CPI: C2000-124450
TITLE: New molecular complex having a gene encoding an interferon linked to a nucleic acid binding agent and a ligand that binds to a cell receptor, useful for targeted delivery of the genes in treating diseases responsive to interferon therapy.
DERWENT CLASS: B04 D16
INVENTOR(S): CARLO, D J; CHIOU, H C
PATENT ASSIGNEE(S): (IMMU-N) IMMUNE RESPONSE CORP
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6069133	A	20000530	(200035)*		28

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 6069133	A	CIP of	US 1996-616023	19960314
			US 1997-819238	19970317

PRIORITY APPLN. INFO: US 1997-819238 19970317; US 1996-616023 19960314
AN 2000-410878 [35] WPIDS
CR 1997-470878 [43]; 2002-105276 [06]
AB US 6069133 A UPAB: 20020301
NOVELTY - A molecular complex comprising a gene encoding an interferon (IFN) releasably linked to a conjugate of a cationic agent that binds the gene and a ligand that binds to an asialoglycoprotein receptor on liver cells, is new.

DETAILED DESCRIPTION - A molecular complex comprising a gene encoding an interferon (IFN) releasably linked to a conjugate of a cationic agent that binds the gene and a ligand that binds to an asialoglycoprotein receptor on liver cells, is new. The gene is operably linked to the thyroxin binding globulin (TBG) promoter, and one or more copies of the alpha-1 microglobulin/bikunin (ABP) enhancer, such that the gene is expressed, processed and secreted from the target cell.

An INDEPENDENT CLAIM is also included for a method of delivering a gene encoding IFN to a target liver cell in a mammal comprising **administering** to the mammal the molecular complex.

ACTIVITY - Immunomodulator; cytostatic; hepatotropic; antiinflammatory; anti-human immunodeficiency virus (HIV).

MECHANISM OF ACTION - Gene therapy; interferon agonist. A 1.0 ml dose of complex solution (pJ7 Omega IFN alpha -P1-ASOR, pJ7 Omega hIFN alpha -P1-ASOR, pJ Omega hIFN alpha SB-P1-ASOR, pJ7 Omega hIFN alpha -nonSB-P1-ASOR, pSVIFN alpha -P1-ASOR and pSVIFN alpha RV-P1-ASOR) was injected into adult female BALB/C mice. Additional control mice received 1.0 ml injections of an identically formulated human growth hormone (hGH) plasmid-containing complex. Blood samples were taken from the animals and serum from samples were analyzed for human **IFN**- alpha **2b** protein by ELISA (enzyme

linked immunosorbent assay). Control animals treated with hGH complex did not produce any measurable human **IFN**- alpha **2b**. Animals treated with the complex solution showed long-term in vivo expression of IFN.

USE - The molecular complex is useful for targeted delivery of genes encoding IFN to selected cells. The molecular complex can be delivered to selected cells in vivo to **treat** a variety of diseases that are responsive to IFN **therapy**. Alternatively, the molecular complex can be delivered to selected cells in vitro to produce recombinant IFN which can be **administered** as exogenous protein to patients in conventional IFN protein **therapy**. IFN is useful in **treating** hairy cell leukemia, condyloma, Kaposi's sarcoma in **AIDS** (**acquired** immune deficiency **syndrome**) patients or type C hepatitis infection.

ADVANTAGE - IFN therapy currently involves **administration** of exogenous IFN to patients on a frequent (e.g. daily) basis. High dosages are often required to achieve a sufficient concentration of IFN in target tissues. In addition, patients often experience a variety of adverse side effects and/or peripheral toxicities associated with systemic delivery of IFN. The molecular complex provides an improved form of IFN replacement therapy. The process employs targeted delivery of genes encoding IFN, therefore it requires a smaller dose and has low toxicity.

Dwg.0/17

L6 ANSWER 8 OF 22 WPIDS (C) 2003 THOMSON DERWENT

ACCESSION NUMBER: 1999-418868 [35] WPIDS
CROSS REFERENCE: 1995-200099 [26]; 1997-297874 [27]; 1998-119930 [11]
DOC. NO. CPI: C1999-123115
TITLE: Alpha-interferon conjugates composition used in the treatment of interferon susceptible conditions.
DERWENT CLASS: A11 A14 A18 A25 A96 B04
INVENTOR(S): GILBERT, C W; PARK-CHO, M
PATENT ASSIGNEE(S): (SCHE) SCHERING CORP; (ENZO-N) ENZON INC
COUNTRY COUNT: 86
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9932139	A1	19990701	(199935)*	EN	35
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW					
ZA 9811590	A	19990831	(199939)		34
US 5951974	A	19990914	(199944)		
AU 9919167	A	19990712	(199950)		
SG 71179	A1	20000321	(200022)		
US 6042822	A	20000328	(200023)		
JP 2000508356	W	20000704	(200037)		37
EP 1039922	A1	20001004	(200050)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
MX 9911862	A1	20000901	(200139)		

HU 2001001532 A2 20010828 (200157)
KR 2001024755 A 20010326 (200161)
AU 739359 B 20011011 (200171)
EP 1039922 B1 20020612 (200239) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
DE 69806055 E 20020718 (200255)
CA 2268433 C 20020730 (200259) EN
NZ 504735 A 20021025 (200274)
ES 2178297 T3 20021216 (200306)

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9932139	A1		WO 1998-US26677	19981216
ZA 9811590	A		ZA 1998-11590	19981217
US 5951974	A	CIP of	US 1993-150643	19931110
		CIP of	US 1994-337567	19941110
			US 1997-994622	19971219
AU 9919167	A		AU 1999-19167	19981216
SG 71179	A1		SG 1998-5535	19981211
US 6042822	A	CIP of	US 1993-150643	19931110
		CIP of	US 1994-337567	19941110
		Cont of	US 1997-994622	19971219
			US 1999-287476	19990406
JP 2000508356	W		WO 1998-US26677	19981216
			JP 1999-533967	19981216
EP 1039922	A1		EP 1998-963947	19981216
			WO 1998-US26677	19981216
MX 9911862	A1		MX 1999-11862	19991216
HU 2001001532	A2		WO 1998-US26677	19981216
			HU 2001-1532	19981216
KR 2001024755	A		KR 2000-706669	20000616
AU 739359	B		AU 1999-19167	19981216
EP 1039922	B1		EP 1998-963947	19981216
			WO 1998-US26677	19981216
DE 69806055	E		DE 1998-606055	19981216
			EP 1998-963947	19981216
			WO 1998-US26677	19981216
CA 2268433	C		CA 1998-2268433	19981216
			WO 1998-US26677	19981216
NZ 504735	A		NZ 1998-504735	19981216
			WO 1998-US26677	19981216
ES 2178297	T3		EP 1998-963947	19981216

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 5951974	A	CIP of	US 5711944
AU 9919167	A	Based on	WO 9932139
US 6042822	A	CIP of	US 5711944
		Cont of	US 5951974
JP 2000508356	W	Based on	WO 9932139
EP 1039922	A1	Based on	WO 9932139
HU 2001001532	A2	Based on	WO 9932139
AU 739359	B	Previous Publ.	AU 9919167

		Based on	WO 9932139
EP 1039922	B1	Based on	WO 9932139
DE 69806055	E	Based on	EP 1039922
		Based on	WO 9932139
CA 2268433	C	Based on	WO 9932139
NZ 504735	A	Based on	WO 9932139
ES 2178297	T3	Based on	EP 1039922

PRIORITY APPLN. INFO: US 1997-994622 19971219; US 1993-150643 19931110; US 1994-337567 19941110; US 1999-287476 19990406

AN 1999-418868 [35] WPIDS

CR 1995-200099 [26]; 1997-297874 [27]; 1998-119930 [11]

AB WO 9932139 A UPAB: 20030124

NOVELTY - Improved alpha -interferon (alpha -IFN) conjugates comprise a non-antigenic polymer covalently bound to a histidine residue of the interferon, for increasing the circulating half-life, is new.

DETAILED DESCRIPTION - A novel pharmaceutical composition comprises a mixture of alpha -IFN polymer conjugate positional isomers, where one of the positional isomers comprises an alpha -IFN covalently conjugated to a non-antigenic polymer at a histidine residue on the alpha -IFN.

INDEPENDENT CLAIMS are also included for the following:

(1) an alpha -IFN-containing composition comprising alpha -IFN polymer conjugates, where at least 15% of the conjugates include covalent attachment of the non-antigenic polymer at a histidine of the alpha -IFN;

(2) a pharmaceutical composition comprising a mixture of alpha **-IFN 2b**-polymer positional isomers, where 30-60% of the positional isomers include a non-antigenic polymer conjugated to the His34 of the alpha -IFN, 7-20% of the positional isomers include a non-antigenic polymer conjugated to the Cys1 of the alpha -IFN and 7-15% of the positional isomers include a non-antigenic polymer conjugated to the Lys121 of the alpha -IFN; and

(3) a method of preparing alpha -IFN conjugates comprising contacting an alpha -IFN with an oxycarbonyl-oxy-N-dicarboximide-activated non-antigenic polymer to facilitate covalent attachment of the non-antigenic polymer at a histidine of the alpha -IFN.

USE - The compositions can be used for **treating** an IFN-susceptible condition in mammals (claimed), e.g. cell proliferation, in particular cancer (e.g. hairy cell leukemia, Kaposi's sarcoma, chronic myelogenous leukemia, multiple myeloma, basal cell carcinoma and malignant melanoma, ovarian cancer, cutaneous T cell lymphoma), and viral infections, e.g. hepatitis A, hepatitis B, hepatitis C, other non-A/non-B hepatitis, herpes virus, Epstein-Barr virus (EBV), cytomegaolvirus (CMV), herpes simplex, human herpes virus type 6 (HHV-6), papilloma, poxvirus, picornavirus, adenovirus, rhinovirus, **human** T lymphotrophic **virus**-type **1** and 2 (**HTLV** **-1**/2), human rotavirus, rabies, retroviruses including HIV, encephalitis and respiratory viral infections. The compositions can also be used to modify various immune responses.

ADVANTAGE - The linkage of the polymer to a His residue in alpha -IFN is relatively labile so that at physiologic pH, the compositions show a relatively smooth onset on activity after **administration** as well as a prolonged duration of effect. This allows **administration** of the compositions in less

frequent doses than with unmodified IFNs. The compositions show reduced or eliminated side effects as compared to conventional alpha -IFN treatment.
Dwg.0/2

L6 ANSWER 9 OF 22 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 2
ACCESSION NUMBER: 1999120875 EMBASE
TITLE: Phase II, randomized, open-label, community-based trial to compare the safety and activity of combination therapy with recombinant interferon-.alpha.2b and zidovudine versus zidovudine alone in patients with asymptomatic to mildly symptomatic HIV infection.
AUTHOR: Krown S.E.; Aeppli D.; Balfour H.H. Jr.
CORPORATE SOURCE: S.E. Krown, Memorial Sloan-Kettering Can. Center, 1275 York Avenue, New York, NY 10021, United States
SOURCE: Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology, (1999) 20/3 (245-254).
Refs: 28
ISSN: 1077-9450 CODEN: JDSRET
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Objectives: To compare, in a community-based **therapeutic** setting, the safety, tolerance, and efficacy of combination **therapy** with recombinant **interferon**-.alpha. **2b** (rIFN.alpha.2b) and zidovudine (ZDV) to ZDV monotherapy. Design: Open-label, two-armed, randomized study. Patients and Methods: Asymptomatic or minimally symptomatic HIV-infected adults without an **AIDS**-defining illness, a CD4 count of 200 to 500 cells/.mu.l, and .ltoreq.6 months of prior ZDV **therapy** received ZDV 100 mg orally five times daily. Patients randomized to rIFN-.alpha.2b received 3 million IU subcutaneously three times weekly for 2 weeks and 5 million IU three times weekly thereafter. The groups were compared with respect to adverse events (AEs), dosing modifications, **treatment** discontinuation, clinical endpoints and changes in CD4 count. A virology substudy compared the **treatments** with respect to HIV viral load and development of ZDV resistance. Results: Between October, 1991 and January, 1993, 139 patients were randomized to combination **therapy** and 117 to ZDV alone. Of AEs reported at any grade, fatigue, myalgias, and sweating occurred significantly more often with combination **therapy** ($p < .001$). Study subjects receiving combination **therapy** showed modest but significantly greater weight loss ($p = .0001$), a significantly higher frequency of any abnormal laboratory test result ($p = .002$), neutropenia ($p = .002$), and leukopenia ($p = .02$), and also required dosage reduction for hematologic toxicity significantly more often ($p < .05$) than those in the ZDV monotherapy arm. No statistically significant differences were found between the groups with respect to development of specific **AIDS**-defining events, overall event rate, time to events, or change in performance status or CD4+ counts, or percentages or development of ZDV resistance. Viral burden,

reflected by serum p24 antigen and quantitative peripheral blood mononuclear cell (PBMC) microcultures, was greater at baseline in the combination **therapy** group. Baseline SI phenotype predicted progression to **AIDS** (p = .004, AHp2), whereas intermediate susceptibility to ZDV predicted development of ZDV resistance (p < .005, AHp2). The annual rate of development of phenotypic resistance to ZDV was 16.8% and was not affected by **administration** of rIFN-.alpha.2b. Conclusions: At the doses and schedule used in this study, the combination of ZDV with rIFN-.alpha.2b was not **therapeutically** superior to ZDV alone and was less well tolerated. The addition of rIFN-.alpha.2b to ZDV did not prevent or delay the development of ZDV resistance.

L6 ANSWER 10 OF 22 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 1999143934 MEDLINE
DOCUMENT NUMBER: 99143934 PubMed ID: 9989342
TITLE: Clinical pharmacokinetics of lamivudine.
AUTHOR: Johnson M A; Moore K H; Yuen G J; Bye A; Pakes G E
CORPORATE SOURCE: Glaxo Wellcome Research and Development, Greenford, England.. maj@glaxowellcome.co.uk
SOURCE: CLINICAL PHARMACOKINETICS, (1999 Jan) 36 (1) 41-66. Ref: 70
Journal code: 7606849. ISSN: 0312-5963.
PUB. COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990517
Last Updated on STN: 19990517
Entered Medline: 19990504

AB Lamivudine (3TC), the negative enantiomer of 2'-deoxy-3'-thiacytidine, is a dideoxynucleoside analogue used in combination with other agents in the **treatment** of **human** immunodeficiency **virus** type **1** (**HIV-1**) infection and as monotherapy in the **treatment** of hepatitis B virus (HBV) infection. Lamivudine undergoes anabolic phosphorylation by intracellular kinases to form lamivudine 5'-triphosphate, the active anabolite which prevents HIV-1 and HBV replication by competitively inhibiting viral reverse transcriptase and terminating proviral DNA chain extension. The pharmacokinetics of lamivudine are similar in patients with HIV-1 or HBV infection, and healthy volunteers. The drug is rapidly absorbed after oral **administration**, with maximum serum concentrations usually attained 0.5 to 1.5 hours after the dose. The absolute bioavailability is approximately 82 and 68% in adults and children, respectively. Lamivudine systemic exposure, as measured by the area under the serum drug concentration-time curve (AUC), is not altered when it is **administered** with food. Lamivudine is widely distributed into total body fluid, the mean apparent volume of distribution (Vd) being approximately 1.3 L/kg following intravenous **administration**. In pregnant women, lamivudine concentrations in maternal serum, amniotic fluid, umbilical cord and neonatal serum are comparable, indicating that the drug diffuses freely across the placenta. In postpartum women lamivudine is secreted into breast milk. The concentration of lamivudine in

cerebrospinal fluid (CSF) is low to modest, being 4 to 8% of serum concentrations in adults and 9 to 17% of serum concentrations in children measured at 2 to 4 hours after the dose. In patients with normal renal function, about 5% of the parent compound is metabolised to the trans-sulphoxide metabolite, which is pharmacologically inactive. In patients with renal impairment, the amount of trans-sulphoxide metabolite recovered in the urine increases, presumably as a function of the decreased lamivudine elimination. As approximately 70% of an oral dose is eliminated renally as unchanged drug, the dose needs to be reduced in patients with renal insufficiency. Hepatic impairment does not affect the pharmacokinetics of lamivudine. Systemic clearance following single intravenous doses averages 20 to 25 L/h (approximately 0.3 L/h/kg). The dominant elimination half-life of lamivudine is approximately 5 to 7 hours, and the in vitro intracellular half-life of its active 5'-triphosphate anabolite is 10.5 to 15.5 hours and 17 to 19 hours in HIV-1 and HBV cell lines, respectively. Drug interaction studies have shown that trimethoprim increases the AUC and decreases the renal clearance of lamivudine, although lamivudine does not affect the disposition of trimethoprim. Other studies have demonstrated no significant interaction between lamivudine and zidovudine or between lamivudine and **interferon**-alpha-**2b**. There is limited potential for drug-drug interactions with compounds that are metabolised and/or highly protein bound.

L6 ANSWER 11 OF 22 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 1998065800 EMBASE
TITLE: Safety profile of interferon-.alpha. therapy.
AUTHOR: Weiss K.
CORPORATE SOURCE: Dr. K. Weiss, Clinic. Trial Design/Analysis Div., Food and Drug Administration, Center for Biologics, 1401 Rockville Pike, Rockville, MD 20892, United States
SOURCE: Seminars in Oncology, (1998) 25/1 SUPPL. (9-13). Refs: 11
ISSN: 0093-7754 CODEN: SOLGAV
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Two forms of recombinant interferon-.alpha. (IFN-1/4a and **IFN**-.alpha.**2b**) have been approved by the Food and Drug **Administration** for a variety of clinical indications, including hairy cell leukemia, hepatitis, **acquired** immunodeficiency **syndrome**-related Kaposi's sarcoma, chronic myelogenous leukemia (IFN-1/4a only), and adjuvant **therapy** for melanoma (IFN-1/4b only), based on their proven clinical efficacy and acceptable safety profiles. The continued postmarketing monitoring of adverse reactions associated with IFN-.alpha. **therapy** has revealed some new toxicities. The most common adverse events associated with IFN-.alpha. **therapy** are flu-like symptoms, fatigue, anorexia, and central nervous system and psychiatric reactions. In particular, the incidence of

depression has only recently been fully appreciated. Some of these side effects, particularly chronic fatigue, anorexia, and neuropsychiatric reactions, may become dose limiting. New approaches to minimize and manage the side effects of IFN-.alpha. **therapy** are needed.

L6 ANSWER 12 OF 22 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 97463299 MEDLINE
DOCUMENT NUMBER: 97463299 PubMed ID: 9322083
TITLE: Interferon-alpha neutralizing antibodies in HIV and chronic HCV patients treated with natural-source human leukocyte-derived interferon-alpha n3.
AUTHOR: Zhao X X; Hua J; Smith T; Ferencz-Biro K; Liao M J; Rashidbaigi A
CORPORATE SOURCE: Interferon Sciences, New Brunswick, NJ 08901-3605, USA.
SOURCE: HUMAN ANTIBODIES, (1997) 8 (3) 129-36.
Journal code: 9711270. ISSN: 1093-2607.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199711
ENTRY DATE: Entered STN: 19971224
Last Updated on STN: 19971224
Entered Medline: 19971105

AB Human leukocyte-derived IFN-alpha n3 (Alferon N Injection) was **administered** subcutaneously to **treat** 20 patients with asymptomatic **human** immunodeficiency **virus** type **1** (**HIV-1**) and 141 patients with chronic hepatitis C virus (HCV) infections. The **treatment** of **HIV-1** and HCV patients, previously untreated with any IFN preparations, did not result in development of neutralizing antibodies to IFN-alpha n3. Among 69 HCV refractory patients who were unresponsive to previous treatment with rIFN-alpha 2b, 2 had neutralizing antibodies to rIFN-alpha **2b** prior to **IFN**-alpha n3 therapy, with no or limited cross-reactivity to IFN-alpha n3. After retreatment with IFN-alpha n3, both patients had detectable neutralizing titers to IFN-alpha n3. Additionally, 2 other patients developed low and transient neutralizing titers to IFN-alpha n3. Interferon subtype specificity of these antibodies was tested against RP-HPLC purified fractions of IFN-alpha n3, as well as rIFN-alpha 2b and rIFN-alpha 8b. Sera from patients previously treated with rIFN-alpha 2b with high antibody titers to rIFN-alpha 2b strongly reacted with the natural **IFN**-alpha **2b**, and to a limited extent with other iFN-alpha subtypes. Neutralizing activity against **IFN** -alpha **2b** was significantly competed out by the presence of a small amount of other interferon subtypes present in IFN-alpha n3. One patient with prior presence of antibodies to **IFN** -alpha **2b** developed a high antibody titer to IFN-alpha 8b with limited reactivity to IFN-alpha n3. Two of the HCV refractory patients with prior neutralizing antibodies to rIFN-alpha **2b** responded to **IFN**-alpha n3 therapy. These data suggest that the presence of neutralizing antibodies to individual IFN-alpha species will not significantly diminish the biological activity and the clinical efficacy of multi-species IFN-alpha n3.

L6 ANSWER 13 OF 22 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 93012464 MEDLINE
DOCUMENT NUMBER: 93012464 PubMed ID: 1397675
TITLE: Combined zidovudine and interferon-alpha 2a therapy in children with acquired immune deficiency syndrome.
AUTHOR: Giovannini M; Zuccotti G V; Biasucci G; Locatelli V; Riva E
CORPORATE SOURCE: Fifth Paediatric Department, University of Milan, Italy.
SOURCE: JOURNAL OF INTERNATIONAL MEDICAL RESEARCH, (1992 Jun) 20 (3) 295-301.
Journal code: 0346411. ISSN: 0300-0605.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199211
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19970203
Entered Medline: 19921123

AB A study was carried out in five children with **acquired** immune deficiency **syndrome** to assess the effect of combined zidovudine/**interferon**-alpha **2a** **therapy** with that of zidovudine given alone on immunological profiles and plasma zidovudine concentrations. Immunoglobulins A, G and M, total and absolute CD4 lymphocyte counts, and p24 antigen concentrations did not differ significantly when children were treated with 300 mg/m2 zidovudine given orally once every 12 h, or with 150 mg/m2 zidovudine plus 1.5 or 3 MIU **interferon** -alpha **2a** given intramuscularly three times weekly. Peak plasma zidovudine concentrations were significantly (P less than 0.05) lower when combined treatment with 150 mg/m2 zidovudine/1.5 MIU **interferon**-alpha **2a** was **administered** compared with 300 mg/m2 zidovudine alone, or combined 150 mg/m2 zidovudine/3 MIU **interferon**-alpha **2a**. The results suggest that combination zidovudine/**interferon** -alpha **2a** therapy may be more efficacious than zidovudine alone and that the normal zidovudine dose may be reduced if **interferon**-alpha **2a** is given in addition, thus reducing the side-effects associated with zidovudine.

L6 ANSWER 14 OF 22 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 91190879 MEDLINE
DOCUMENT NUMBER: 91190879 PubMed ID: 1826454
TITLE: Interferon-alpha 2a in the treatment of acquired immunodeficiency syndrome-related Kaposi's sarcoma.
AUTHOR: Evans L M; Itri L M; Campion M; Wyler-Plaut R; Krown S E; Groopman J E; Goldsweig H; Volberding P A; West S B; Mitsuyasu R T; +
CORPORATE SOURCE: Hoffmann-La Roche, Nutley, New Jersey.
SOURCE: JOURNAL OF IMMUNOTHERAPY, (1991 Feb) 10 (1) 39-50.
Journal code: 9102704. ISSN: 1053-8550.
PUB. COUNTRY: United States
DOCUMENT TYPE: (CLINICAL TRIAL)
(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(MULTICENTER STUDY)
LANGUAGE: English

FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199105
ENTRY DATE: Entered STN: 19910602
Last Updated on STN: 19980206
Entered Medline: 19910510

AB In a series of studies, recombinant **interferon**-alpha **2a** (rIFN alpha 2a, Roferon-A) was **administered** alone (273 men) or combined with vinblastine (91 men) to patients with acquired immunodeficiency syndrome (AIDS)-related Kaposi's sarcoma (KS). Patients were treated with daily doses of rIFN alpha 2a ranging from 3 to 54 million international units (I.U.) **administered** intramuscularly. A dose of 36 million I.U. daily for approximately 10 weeks followed by a three times weekly maintenance schedule with the same dose resulted in the best overall therapeutic benefit. An escalating-dose regimen of 3, 9, and 18 million I.U. daily, each for 3 days, followed by 36 million I.U. daily, produced equivalent therapeutic benefit with amelioration of acute toxicity in some patients. Response was more likely in patients without a history of opportunistic infection or B symptoms (fever, night sweats, or weight loss). Response rate increased with increasing baseline CD4 lymphocyte count and was 45.5% in patients with a CD4 count of greater than 400/mm3. Responding patients with a CD4 count of greater than 200/mm3 had a distinct survival advantage over patients who had similar CD4 counts but whose tumors did not regress with therapy. The addition of vinblastine increased toxicity and did not improve the response rate or prolong survival. Side effects included fatigue, fever, chills, myalgias, headaches, anorexia, nausea, diarrhea, and dizziness. Mild abnormalities in hematologic and liver function tests occurred in some patients. Most adverse effects diminished or resolved with continued therapy. We conclude that rIFN alpha 2a offers important **therapeutic** benefit in a select group of patients with **AIDS**-related KS.

L6 ANSWER 15 OF 22 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 91136196 MEDLINE
DOCUMENT NUMBER: 91136196 PubMed ID: 2178336
TITLE: Alpha interferon (2b) in combination with zidovudine for the treatment of presymptomatic feline leukemia virus-induced immunodeficiency syndrome.
AUTHOR: Zeidner N S; Myles M H; Mathiason-DuBard C K; Dreitz M J; Mullins J I; Hoover E A
CORPORATE SOURCE: Department of Pathology, Colorado State University, Fort Collins 80523.
CONTRACT NUMBER: NO1 AI 72663 (NIAID)
SOURCE: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1990 Sep) 34 (9) 1749-56.
Journal code: 0315061. ISSN: 0066-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199103
ENTRY DATE: Entered STN: 19910405
Last Updated on STN: 19970203
Entered Medline: 19910319

AB The **therapeutic** efficacies of human recombinant alpha interferon (IFN-alpha), IFN-alpha plus zidovudine (AZT), and AZT

alone were evaluated in presymptomatic cats with established feline leukemia virus (FeLV)-**acquired** immunodeficiency **syndrome** (FAIDS) infection and high levels of persistent antigenemia. Subcutaneous injection of 1.6 x 10(6) U of human recombinant **IFN**-alpha **2b** per kg delivered peak concentrations in plasma of 3,600 U/ml at 2 h postadministration with a half-life of elimination of 2.9 h. This dosage of IFN-alpha could be delivered to cats for up to 12 weeks without significant clinical toxicity. Oral **administration** of AZT (20 mg/kg three times daily) resulted in peak concentrations in plasma of 3 micrograms/ml at 2 h with a half-life of elimination of approximately 1.60 h. Treatment of FeLV-FAIDS-infected cats with IFN-alpha, either alone or in combination with orally **administered** AZT, resulted in significant decreases in circulating p27 core antigen beginning 2 weeks after the initiation of therapy. AZT alone had no effect on circulating virus antigen. Depending upon whether high (1.6 x 10(6) U/kg)- or low (1.6 x 10(4) to 1.6 x 10(5) U/kg)-dosage IFN-alpha was used, cats became refractory to therapy 3 or 7 weeks after the beginning of treatment. At these times, IFN-alpha-treated animals developed antibodies to IFN-alpha that were neutralizing, specific for human recombinant IFN-alpha, and dose dependent in magnitude. The results of this study indicate that human recombinant IFN-alpha is effective in reducing circulating virus antigenic load in cats persistently infected with FeLV-FAIDS.(ABSTRACT TRUNCATED AT 250 WORDS)

L6 ANSWER 16 OF 22 MEDLINE DUPLICATE 8

ACCESSION NUMBER:	90262043 MEDLINE
DOCUMENT NUMBER:	90262043 PubMed ID: 1971504
TITLE:	Interferon-alpha with zidovudine: safety, tolerance, and clinical and virologic effects in patients with Kaposi sarcoma associated with the acquired immunodeficiency syndrome (AIDS).
COMMENT:	Erratum in: Ann Intern Med 1990 Aug 15;113(4):334
AUTHOR:	Krown S E; Gold J W; Niedzwiecki D; Bundow D; Flomenberg N; Gansbacher B; Brew B J
CORPORATE SOURCE:	Memorial Sloan-Kettering Cancer Center, New York, New York.
CONTRACT NUMBER:	AI-27669 (NIAID)
SOURCE:	ANNALS OF INTERNAL MEDICINE, (1990 Jun 1) 112 (11) 812-21. Journal code: 0372351. ISSN: 0003-4819.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	(CLINICAL TRIAL) Journal; Article; (JOURNAL ARTICLE) (RANDOMIZED CONTROLLED TRIAL)
LANGUAGE:	English
FILE SEGMENT:	Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH:	199006
ENTRY DATE:	Entered STN: 19900720 Last Updated on STN: 20000303 Entered Medline: 19900628

AB OBJECTIVE: To evaluate safety, tolerance, and potential efficacy of interferon-alpha and zidovudine combination **therapy** in patients with Kaposi sarcoma and the **acquired** immunodeficiency **syndrome** (**AIDS**). DESIGN: Open, phase-I study with randomization between two preparations of

interferon-alpha. SETTING: Outpatient clinic of a cancer research center. PATIENTS: Forty-three patients with Kaposi sarcoma associated with AIDS. INTERVENTIONS: Patients were treated with interferon-alpha, 4.5, 9, or 18 million U/d, and zidovudine, 100 or 200 mg orally every 4 hours. MEASUREMENTS AND MAIN RESULTS: Neutropenia was the major dose-limiting toxicity. Fatigue, liver enzyme elevation, anemia, and thrombocytopenia were dose-limiting in some patients. Maximum tolerated dosages for **interferon** -alpha **2a** with zidovudine, respectively, were 4.5 million U/d with 200 mg every 4 hours or 18 million U/d with 100 mg every 4 hours. An interferon-alpha n1 [corrected] dosage of 9 million U/d with zidovudine dosages of either 100 or 200 mg every 4 hours induced dose-limiting toxicity in most patients. Of 37 evaluable patients, 17 (46%; 95% CI, 30% to 62%) showed complete or partial tumor regression. Antitumor effects occurred more frequently in patients with baseline CD4 counts above 200 x 10(6) cells/L (65%) than in patients with lower baseline counts (30%, P = 0.05). Effects on CD4 cells were related to both initial CD4 count and interferon dose. Increased skin test reactivity and decreased serum human immunodeficiency virus (HIV) p24 antigen and virus recovery from blood cells were seen. CONCLUSIONS: Combined **therapy** with interferon-alpha and zidovudine can be safely **administered** to patients with **AIDS** and Kaposi sarcoma. The observed effects on tumor growth, HIV replication, and immune function support further studies of the combination in patients at various stages of HIV infection.

L6 ANSWER 17 OF 22 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 90343411 EMBASE
DOCUMENT NUMBER: 1990343411
TITLE: Responsiveness of classical Kaposi's sarcoma to recombinant interferon alpha 2b treatment.
AUTHOR: Monti M.; Barbareschi M.; Angius A.; Caputo R.
CORPORATE SOURCE: First Department of Dermatology, University of Milan, Milan, Italy
SOURCE: Journal of Dermatological Treatment, (1990) 1/4 (209-210).
ISSN: 0954-6634 CODEN: JDTREY
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
016 Cancer
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB Low doses of recombinant **interferon** alpha **2b** were used to **treat** two patients with Kaposi's sarcoma not associated with **AIDS**. Clinical benefit was obtained after a few months in both cases. In on case dynamic telethermography demonstrated regression of the disease after 9 months of **treatment**. No serious side-effects were observed during interferon **administration**. We conclude that recombinant **interferon** alpha **2b** could be considered a **treatment** of choice for Kaposi's sarcoma not associated with **AIDS**.

L6 ANSWER 18 OF 22 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1989:7504 BIOSIS

DOCUMENT NUMBER: BA87:7504
TITLE: INTERFERON THERAPY OF AIDS-ASSOCIATED KAPOSI'S SARCOMA AND DISSEMINATED MALIGNANT MELANOMA.
AUTHOR(S): STADLER R; BRATZKE B; MAYER DA SILVA A; ORFANOS C E
CORPORATE SOURCE: UNIV.-HAUTKLINIK POLIKLINIK, KLINIKUM STEGLITZ, HINDENBURGDAMM 30, D-1000 BERLIN 45, W. GER.
SOURCE: ONKOLOGIE, (1988) 11 (4), 166-176.
CODEN: ONKOD2. ISSN: 0378-584X.
FILE SEGMENT: BA; OLD
LANGUAGE: German

AB Since 1980, disseminated Kaposi's sarcoma has been occurring in new epidemic proportions with a rapid clinical course in risk populations. Sixteen cases were under **therapy** and close surveillance from 1982 to 1986. Eight are still under **therapy**. In disseminated Kaposi's sarcoma with **acquired** immune deficiency **syndrome** (**AIDS**) our experience was encouraging. Following systemic, long-term **treatment** with recombinant .alpha.**2a** **interferon** we observed complete remission of the lesions in 2 cases, partial remission and stabilization of the disease in 3 cases, at least temporary stabilization of the disease in 3 cases and progressive disease in 8 cases. Systemic rIFN-.alpha.2a **therapy** was well tolerated; its long-term **administration** in patients with a relatively good immune status has an obviously beneficial effect on the course of Kaposi's sarcoma. In metastatic malignant melanoma Stage IV the results were only moderately encouraging. Regression of cutaneous metastases in 1 case and long-term stabilization of the disease in another patient point to antitumor activity of interferon in disseminated malignant melanoma. However, the **administration** of rIFN-.alpha.2a in earlier stages appears more promising.

L6 ANSWER 19 OF 22 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1989:223835 BIOSIS
DOCUMENT NUMBER: BA87:115452
TITLE: A RANDOMIZED PLACEBO-CONTROLLED TRIAL OF RECOMBINANT HUMAN INTERFERON ALPHA 2A IN PATIENTS WITH AIDS.
AUTHOR(S): INTERFERON ALPHA STUDY GROUP (USA)
CORPORATE SOURCE: INQ.: GERALD H. FRIEDLAND, MONTEFIORE MED. CENT., 111 EAST 210TH ST., BRONX, N.Y. 10467, USA.
SOURCE: J ACQUIRED IMMUNE DEFIC SYNDR, (1988) 1 (2), 111-118.
CODEN: JAISET.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB We performed a randomized, double-blind, placebo-controlled trial to assess the tolerance and efficacy of recombinant human **interferon** alpha **2a** (Roferon A) in patients with **acquired** immunodeficiency **syndrome** (**AIDS**) without Kaposi's sarcoma. A total of 67 patients were enrolled in five medical centers from October 1983 through April 1986, and received either placebo, 3 million units, or 36 million units of interferon alpha three times a week for 12 weeks. There were no significant differences in median survival, frequency of development of opportunistic infections, median T4-cell counts, or serum p24 antigen levels during **therapy** among the three groups. There was a significant increase in weight in the 3-million-unit group compared with 36-million-unit and placebo groups. Adverse reactions were common in the two interferon groups,

but did not differ significantly from the placebo group. Neither significant **therapeutic** benefit nor adverse reaction was demonstrated in this study to be associated with interferon-alpha **administration**. This study underlines the value of randomized, double-blind, placebo-controlled studies to address specific issues of drug efficacy and toxicity.

L6 ANSWER 20 OF 22 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1987:169949 BIOSIS
DOCUMENT NUMBER: BA83:88390
TITLE: INCIDENCE AND CLINICAL SIGNIFICANCE OF NEUTRALIZING ANTIBODIES IN PATIENTS RECEIVING RECOMBINANT INTERFERON ALFA-2A BY INTRAMUSCULAR INJECTION.
AUTHOR(S): ITRI L M; CAMPION M; DENNIN R A; PALLERONI A V; GUTTERMAN J U; GROOPMAN J E; TROWN P W
CORPORATE SOURCE: HOFFMANN-LA ROCHE INC., 340 KINGSLAND ST., NUTLEY, N.J. 07110, USA.
SOURCE: CANCER (PHILA), (1987) 59 (3 SUPPL), 668-674. CODEN: CANCAR. ISSN: 0008-543X.
FILE SEGMENT: BA; OLD
LANGUAGE: English
AB More than 1600, patients with neoplastic disorders have received recombinant human **interferon** alfa-**2a** (Roferon-A, Hoffmann-La Roche, Nutley, NJ) as part of ongoing or completed clinical trials. In this report, the efficacy of **interferon** alfa-**2a therapy** was compared with the incidence of antibodies to this interferon in 617 patients who received the drug by intramuscular **administration**. Antibody measurements were performed using a highly sensitive enzyme immunoassay, and an interferon antiviral neutralization bioassay. Partial or complete remission occurred in 28% (43 of 152) of the antibody-positive patients, and in 24% (112 of 465) of the antibody-negative patients (P = 0.33). The highest incidence of antibody formation occurred among patients with renal cell carcinoma and **acquired** immune deficiency **syndrome** (**AIDS**)-related Kaposi's sarcoma (44% and 34%, respectively). Both the duration of **treatment** and length of survival were significantly longer for antibody-positive than for antibody-negative patients. No significant intergroup differences emerged for response rates or for time to onset or duration of **therapeutic** response. When results from the above assays were compred to those used for the detection of antibodies to recombinant **interferon** alfa-**2b** (Intron A, Schering-Plough Inc., Kenilworth, NJ), the immunoradiometric assay method was determined to be seriously deficient for determination of antibody incidence. This decreased assay sensitivity may account for the reportedly lower incidence of antibodies to recombinant alfa-**2b interferon**.

L6 ANSWER 21 OF 22 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 9
ACCESSION NUMBER: 1987:169908 BIOSIS
DOCUMENT NUMBER: BA83:88349
TITLE: TREATMENT OF KAPOSI'S SARCOMA WITH INTERFERON ALPHA-2B INTRON A.
AUTHOR(S): VOLBERDING P A; MITSUYASU R T; GOLANDO J P; SPIEGEL R J
CORPORATE SOURCE: ONCOL. CLIN. RES., SCHERING CORP., 2000 GALLOPING

HILL ROAD, KENILWORTH, N.J. 07033, USA.
SOURCE: CANCER (PHILA), (1987) 59 (3 SUPPL), 620-625.
CODEN: CANCAR. ISSN: 0008-543X.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB The activity of the alpha interferons against **AIDS**-related Kaposi's sarcoma (KS) has been demonstrated in numerous clinical trials. Unfortunately, most reports have involved small patient cohorts and a variety of dosages and schedules of **administration**. We report here a series of Phase II trials with **interferon** alfa-**2b** (Intron A, Schering Corp., Kenilworth, NJ) involving 114 patients using three dose regimens. Patients received 50 .times. 106 IU/m2 intravenously (high dose), 30 .times. 106 IU/m2 subcutaneously (intermediate dose), or 1 .times. 106 IU/m2 subcutaneously (low dose). Clinical responses were seen in all regimens and, overall, 35% of the patients obtained complete or partial remissions. The response rates in the low-, intermediate-, and high-dose groups were 33%, 28%, and 45%, respectively. In addition, high-dose **therapy** was associated with more rapid time to response. Patient with low-stage (I or II) disease and those who lack B symptoms were more likely to respond to **therapy**; i.e., response rates for patients without B symptoms were 38%, 44%, and 60% in the low-, intermediate-, and high-dose groups, respectively. Seventy (61%) patients had died at the time of data collection, with a median survival of 15 months. Disease stage and the presence of B symptoms significantly affected mortality. Responders enjoyed significantly longer survival ($P < 0.10$) than did nonresponders both overall and when adjusted for disease stage. **Interferon** alfa-**2b** was generally well tolerated, although almost all patients experienced flu-like symptoms. No life-threatening toxicities occurred and only six (6%) patients discontinued **treatment** due to adverse reactions. No significant improvement in immunologic parameters was detected during this study. These studies suggest that, in this disease setting, **interferon** alfa-**2b** may be acting through direct antiproliferative effects rather than as an immunomodulator, and higher doses appear to be more effective than very low doses.

L6 ANSWER 22 OF 22 JAPIO COPYRIGHT 2003 JPO
ACCESSION NUMBER: 2000-256211 JAPIO
TITLE: HIV MEDICINE
INVENTOR: LAUGHLIN MARK A; GLUE PAUL W; STALGIS CARLOS O
PATENT ASSIGNEE(S): SCHERING PLOUGH CORP
PATENT INFORMATION:

PATENT NO	KIND	DATE	ERA	MAIN IPC
JP 2000256211	A	20000919	Heisei	A61K038-21

APPLICATION INFORMATION
STN FORMAT: JP 2000-55695 20000301
ORIGINAL: JP2000055695 Heisei
PRIORITY APPLN. INFO.: US 1999-260388 19990302
PRIORITY APPLN. INFO.: US 1999-268521 19990312
PRIORITY APPLN. INFO.: US 1999-288358 19990408
PRIORITY APPLN. INFO.: US 1999-454004 19991203
SOURCE: PATENT ABSTRACTS OF JAPAN (CD-ROM), Unexamined

Applications, Vol. 2000

AN 2000-256211 JAPIO
AB PROBLEM TO BE SOLVED: To provide a medicine for lowering the level of HIV-1 RNA.
SOLUTION: This medicine composition comprises only a **therapeutically** effective amount of PEG-interferon-α or the PEG-interferon-α and a **therapeutically** effective amount of an anti-**HIV-1** medicine or a **therapeutically** effective amount of ribavirin, and is used for **treating** the infection of **HIV-1** in adult patients and child patients. The patients include persons who are **therapeutically** still not **treated** or persons who have **therapeutically** been **treated**. The PEG-interferon-α is preferably PEG **interferon**-α-**2b**, and may be **administered** together with the ribavirin, IL-2, IL-12 or pentafuside. The anti-**HIV-1** medicine includes HAART.
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(FILE 'MEDLINE' ENTERED AT 09:16:52 ON 13 JUN 2003)

L7	1779	SEA	FILE=MEDLINE ABB=ON	PLU=ON	"INTERFERON ALFA-2A"/CT
L8	2582	SEA	FILE=MEDLINE ABB=ON	PLU=ON	"INTERFERON ALFA-2B"/CT
L9	4181	SEA	FILE=MEDLINE ABB=ON	PLU=ON	L7 OR L8
L10	32746	SEA	FILE=MEDLINE ABB=ON	PLU=ON	HIV-1/CT
L11	31	SEA	FILE=MEDLINE ABB=ON	PLU=ON	L9 AND L10
L12	12	SEA	FILE=MEDLINE ABB=ON	PLU=ON	L11 AND ADMINISTRATION & DOSAGE/CT

L12 ANSWER 1 OF 12 MEDLINE
AN 1999133597 MEDLINE
TI Low dose oral interferon alpha 2a in HIV-1 seropositive patients: a double-blind, placebo-controlled trial.
AU Wright S E; Hutcheson D P; Cummins J M
SO BIOTHERAPY, (1998) 11 (4) 229-34.
Journal code: 8903031. ISSN: 0921-299X.
AB Low dose oral interferon alpha has been shown to be of benefit in viral disease in animals. In a double-blind, placebo-controlled trial, 177 patients seropositive for HIV-1 were randomly assigned to receive placebo or recombinant human interferon alpha 2a (rIFN alpha). Endpoints were survival, alteration of disease classification, performance, and changes in CD4+ T cell numbers. There was a trend for improved survival in the group receiving rIFN alpha at the dose of 1.0 IU/lb. The changes in disease classification or in weight were not significantly different. Performance was improved to a greater extent (p=0.1) in the patients who received the two higher rIFN alpha dosages (1.0 IU/lb and 10.0 IU/lb) at 6 months. In addition, the CD4+ T cell count was improved only in the 1.0 IU/lb dose treatment group at 6 months. Treatment with low dose oral interferon at 1.0 IU/lb was associated with improved CD4+ T cell count, performance and a trend toward enhanced survival in HIV seropositive patients. These differences were, however, not statistically significant. A larger study, with better return rate, will be needed to determine whether low dose, oral interferon alpha is actually beneficial for these patients.

L12 ANSWER 2 OF 12 MEDLINE

AN 1998063663 MEDLINE
TI Safety and antiviral activity of combination therapy with zidovudine, zalcitabine, and two doses of interferon-alpha2a in patients with HIV. AIDS Clinical Trials Group Study 197.
AU Fischl M A; Richman D D; Saag M; Meng T C; Squires K E; Holden-Wiltse J; Meehan P M
SO JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES AND HUMAN RETROVIROLOGY, (1997 Dec 1) 16 (4) 247-53.
Journal code: 9501482. ISSN: 1077-9450.
AB We conducted a three-arm, randomized, phase II study to evaluate the combination of zidovudine (600 mg/day) and zalcitabine (2.25 mg/day) alone or with one of two interferon-alpha2a doses (1 mIU or 6 mIU daily). Primary study endpoints included toxicity and changes from baseline for plasma HIV-1 RNA, CD4 cells, and quantitative microculture at weeks 8 and 24. Sixty-three patients with HIV infection and <400 CD4 cells/mm3 were enrolled; four patients discontinued therapy within 2 weeks. Adverse event rates were 37%, 32%, and 60%, respectively, for the nucleoside, 1-mIU interferon, and 6-mIU interferon combination groups. Increasing doses of interferon resulted in significantly greater hematologic toxicity ($p = 0.03$) and peripheral neuropathy ($p = 0.02$). Plasma HIV-1 RNA reductions were noted across all treatment groups at week 8 ($p < 0.001$) but only for the nucleoside and 1-mIU interferon combination groups at week 24 ($p < 0.001$). Mean reductions in HIV-1 RNA at week 8 were 0.94, 1.29, and 1.40 log10, respectively, for the nucleoside, 1-mIU interferon, and 6-mIU interferon combination groups ($p = 0.05$); no differences were noted at week 24. No differences in CD4 cell counts were seen. The addition of interferon-alpha2a to zidovudine and zalcitabine resulted in transient enhanced decreases in viral load and increased toxicity.

L12 ANSWER 3 OF 12 MEDLINE
AN 96142199 MEDLINE
TI Continuous low-dose interferon-alpha therapy for HIV-related immune thrombocytopenic purpura.
AU Northfelt D W; Charlebois E D; Mirda M I; Child C; Kaplan L D; Abrams D I
SO JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES AND HUMAN RETROVIROLOGY, (1995 Jan 1) 8 (1) 45-50.
Journal code: 9501482. ISSN: 1077-9450.
AB Our objective was to examine the efficacy and toxicity of continuous, low-dose interferon-alpha therapy for human immunodeficiency virus-related immune thrombocytopenic purpura (HIV-ITP) in a Phase II clinical trial overseen by a community-based consortium of physicians conducting clinical trials in HIV-related diseases. Sixteen patients with HIV-ITP defined by prospective clinical criteria were enrolled; the majority had failed other therapies for HIV-ITP. Baseline and serial measurements were made of platelet counts, complete blood counts, serum chemistries, platelet-associated immunoglobulin, and CD4+ T-lymphocyte counts; subjective symptoms and bleeding were recorded. Three million units of interferon-alpha 2b were self-administered by subcutaneous injection every Monday, Wednesday, and Friday for 16 weeks. Thirteen participants were evaluable for response. One obtained a complete response, eight had partial responses, and four had no response to interferon-alpha therapy. The mean absolute platelet count of the group rose from 15.5 x 10(9)/L at baseline to 47.3 x 10(9)/L at 2 weeks and remained in this range for the duration of

the study. CD4+ T-lymphocyte counts and serum chemistries did not change significantly during therapy. Ability to detect platelet-associated immunoglobulin did not change in a predictable manner in relation to platelet count response. Hematologic toxicity was limited to one episode of granulocytopenia, which resolved after a lowering of zidovudine dosage.. Subjective toxicities were mild and tolerable, and minor bleeding problems improved in all participants so affected. Low-dose, continuous therapy with interferon-alpha resulted in meaningful increases in the platelet counts of the majority of study participants with HIV-ITP. Interferon-alpha was safe and tolerable for most participants with HIV-ITP at the dosage and schedule employed in this study. Interferon-alpha for clinically significant thrombocytopenia and who have failed to respond to zidovudine.

L12 ANSWER 4 OF 12 MEDLINE
AN 96053657 MEDLINE
TI Use of recombinant interferon-alpha in human immunodeficiency virus (HIV)-infected individuals.
AU Rivero J; Limonta M; Aguilera A; Fraga M; Lopez Saura P
SO BIOTHERAPY, (1994) 8 (1) 23-31.
Journal code: 8903031. ISSN: 0921-299X.
AB RATIONALE AND OBJECTIVE: Interferon alpha (IFN-alpha) has anti-retroviral activity and is a possible HIV infection-limiting factor. The aim of this work is to prevent or delay disease progression in asymptomatic Human Immunodeficiency Virus (HIV) carriers. DESIGN AND INTERVENTIONS: Recombinant IFN alpha-2b (3 x 10(6) IU 3 times weekly) was compared to no treatment (control) in a randomized trial. Endpoints were: (i) appearance of any CDC group IV symptoms and (ii) disease progression (which excluded shifts to group IVC2 or reversible IVA, or IVB). The trial lasted from October 1987 to February 1992. SETTING: The trial was performed at the "Santiago de las Vegas" sanatorium, a specialized institution for the care of HIV-infected and AIDS patients. POPULATION: Subjects were anti-HIV-1 seropositive, Western blot-confirmed, asymptomatic (CDC group II), or with generalized lymphadenopathies (CDC group III). The groups had 79 (control) and 71 (IFN) patients. MAIN RESULTS: Long-term IFN-alpha treatments significantly reduced the proportion of patients who shifted to any group IV (control: 46/79; IFN: 14/71; $p < 0.001$) or developed AIDS (control: 27/79; IFN: 12/71; $p < 0.05$). IFN also delayed progression to AIDS (95% confidence interval for 0.5 probability of progression) from 67-83 to 116-180 months after infection. The IFN group had significantly less opportunistic infections and non-infectious complications. CD4 cell count and hemoglobin decreased in the control but not in the IFN group. Fewer IFN-treated patients developed positive serum HIV antigen detection. CONCLUSION: IFN alpha treatment during the early stages of infection seems to be beneficial to the patients.

L12 ANSWER 5 OF 12 MEDLINE
AN 94312547 MEDLINE
TI Combination therapy for infection due to human immunodeficiency virus type 1.
AU Caliendo A M; Hirsch M S
SO CLINICAL INFECTIOUS DISEASES, (1994 Apr) 18 (4) 516-24. Ref: 91
Journal code: 9203213. ISSN: 1058-4838.
AB The preliminary results of the Concorde trial demonstrated the transient clinical benefit of monotherapy with zidovudine (AZT) in

asymptomatic persons infected with human immunodeficiency virus type 1 (HIV-1). This result, which has been widely disseminated and discussed, was predictable given the previous demonstration of the development of resistance to AZT in isolates from individuals receiving prolonged treatment with the drug and given the finding that didanosine (ddI) is more efficacious than continued therapy with AZT in individuals who have received > or = 6 months of AZT monotherapy. On the basis of these findings, interest in combinations of antiretroviral agents has continued to grow. Many in vitro studies of nucleoside and nonnucleoside inhibitors of reverse transcriptase combined with interferon-alpha or inhibitors of protease have been published. In addition, numerous clinical trials of various combinations have been completed or are under way. Dr. Martin Hirsch and his colleagues at the Massachusetts General Hospital have been among the leaders of this effort. He and Dr. Angela Caliendo review, in this AIDS Commentary, the current state of our knowledge regarding the potential utility of combination therapy for infection with HIV-1.

L12 ANSWER 6 OF 12 MEDLINE
AN 94184273 MEDLINE
TI Allogeneic bone marrow transplantation combined with multiple anti-HIV-1 treatment in a case of AIDS.
AU Contu L; La Nasa G; Arras M; Pizzati A; Vacca A; Carcassi C; Ledda A; Boero R; Orru S; Pintus A; +
SO BONE MARROW TRANSPLANTATION, (1993 Dec) 12 (6) 669-71.
Journal code: 8702459. ISSN: 0268-3369.
AB A 25-year-old woman with AIDS was submitted to HLA-identical allogeneic BMT after cytoablation with busulphan and cyclophosphamide and combined anti-HIV-1 therapy with zidovudine, IFN-alpha 2 and anti-HIV-1-specific T cell clones. Marrow engraftment occurred after 18 days and tests for HIV-1 were negative after 30 days but the hematologic reconstitution of the patient was poor. A second BM infusion from the same donor was ineffective and treatment with GM-CSF only induced a transient increase of the blood cell count, suggesting iatrogenic damage to the BM microenvironment. The development of ARDS led to the death of the patient 10 months after transplantation. Post-mortem investigation did not reveal any active infections and PCR on autopsy tissues was negative for HIV-1.

L12 ANSWER 7 OF 12 MEDLINE
AN 94145746 MEDLINE
TI Increased efficacy of human natural interferon alpha (IFN-alpha n3) versus human recombinant IFN-alpha 2 for inhibition of HIV-1 replication in primary human monocytes.
AU Fan S X; Skillman D R; Liao M J; Testa D; Meltzer M S
SO AIDS RESEARCH AND HUMAN RETROVIRUSES, (1993 Nov) 9 (11) 1115-22.
Journal code: 8709376. ISSN: 0889-2229.
AB Natural IFN-alpha n3, a purified mixture of many different natural IFN alpha species, was 10- to 100-fold more effective than equal concentrations of human rIFN-alpha 2b or rIFN-alpha 2a for inhibition of HIV replication in primary human monocytes. This difference was highly reproducible in multiple side-by-side experiments using the identical HIV-1 inoculum and the same monocyte target cells: natural IFN-alpha n3 was more effective than rIFN-alpha 2b at lower concentrations for protection against a constant HIV-1 inoculum; cells treated with natural IFN-alpha n3 were protected against a greater HIV-1 challenge than were cells

treated with the same concentration of rIFN-alpha 2b. Fractionation of natural IFN-alpha n3 by reversed-phase high-pressure liquid chromatography (RP-HPLC) showed that most antiviral activity for HIV localized to discrete and reproducible peaks. The RP-HPLC peak that contained purified natural IFN-alpha 2b was the least effective fraction. These data suggest heterogeneity among IFN-alpha species for antiviral activity against HIV and may provide a molecular basis for more effective IFN-alpha therapy.

L12 ANSWER 8 OF 12 MEDLINE
AN 93305217 MEDLINE
TI Low-dose oral recombinant interferon-alpha A in patients with HIV-1 infection: a blinded pilot study.
AU Sperber S J; Gocke D J; Haberzettl C A; Pestka S
SO AIDS, (1993 May) 7 (5) 693-7.
Journal code: 8710219. ISSN: 0269-9370.
AB OBJECTIVE: To evaluate the efficacy of low-dose oral recombinant interferon-alpha (IFN-alpha A) on clinical parameters, body weight, CD4+ lymphocyte counts and natural killer cell cytolytic activity in HIV-infected patients. DESIGN: Blinded crossover trial with controls for the protein and diluent components of the drug preparation. SETTING: Medical school outpatient referral center. PATIENTS, PARTICIPANTS: Eight patients with HIV-1 infection and a CD4+ lymphocyte count between 150 and 600 x 10(6)/l. Concurrent use of zidovudine was permitted. INTERVENTIONS: Patients received (daily, by mouth) 10 ml of a study solution of 2.5% albumin for 6 weeks, 150 IU IFN-alpha A for 6 weeks, and normal saline for 6 weeks. MAIN OUTCOME MEASURES: After two baseline visits, clinical assessments, vital signs, body weight, and laboratory tests, including enumeration of number and percentage of CD4+ and CD8+ lymphocytes and natural killer cell cytolytic activity, were performed every 3 weeks. Complete physical examinations were conducted every 6 weeks. RESULTS: No significant clinical or laboratory changes were observed during treatment with IFN-alpha A. Peak CD4+ lymphocyte counts were achieved at baseline in one patient, during albumin treatment in two patients, during IFN-alpha A treatment in one patient, and during saline treatment in four patients. All patients remained HIV-seropositive. Treatments were well-tolerated. CONCLUSION: This blinded pilot study of orally administered IFN-alpha A (150 IU daily for 6 weeks) did not demonstrate clinical benefit in HIV-infected patients.

L12 ANSWER 9 OF 12 MEDLINE
AN 92235477 MEDLINE
TI Zidovudine-interferon-alpha combination therapy in patients with advanced human immunodeficiency virus type 1 infection: biphasic response of p24 antigen and quantitative polymerase chain reaction.
AU Edlin B R; Weinstein R A; Whaling S M; Ou C Y; Connolly P J; Moore J L; Bitran J D
SO JOURNAL OF INFECTIOUS DISEASES, (1992 May) 165 (5) 793-8.
Journal code: 0413675. ISSN: 0022-1899.
AB In an open-label dose-ranging pilot trial, 13 homosexual men with human immunodeficiency virus type 1 (HIV-1) p24 antigenemia after at least 6 weeks of zidovudine monotherapy were continued on zidovudine and given interferon-alpha, 1.25-7.5 x 10(6) units/m2 subcutaneously three times/week. Plasma p24 antigen levels demonstrated a biphasic response, falling initially in 11 patients by a mean of 50% (95% confidence interval, 36%-64%; P = .001) at a median of 11 weeks, but

rising steadily thereafter (P = .001). CD4+ cell counts fell by a mean of 7.1 cells/mm3/week (P = .01). Higher initial CD4+ counts predicted greater p24 antigen reductions. At higher interferon doses no greater reductions in p24 antigen occurred, but side effects were more severe and CD4+ lymphocyte counts fell faster. Polymerase chain reaction quantification of HIV-1 DNA in 3 patients showed a biphasic pattern paralleling the p24 antigen response. In sum, although evidence of short-term effects was found, the combination showed no evidence of lasting antiviral activity beyond that achieved with zidovudine alone in patients with advanced HIV-1 infection.

L12 ANSWER 10 OF 12 MEDLINE
AN 91277494 MEDLINE
TI A phase I/II trial of zidovudine, interferon-alpha, and granulocyte-macrophage colony-stimulating factor in the treatment of human immunodeficiency virus type 1 infection.
AU Davey R T Jr; Davey V J; Metcalf J A; Zurlo J J; Kovacs J A; Falloon J; Polis M A; Zunich K M; Masur H; Lane H C
SO JOURNAL OF INFECTIOUS DISEASES, (1991 Jul) 164 (1) 43-52. Journal code: 0413675. ISSN: 0022-1899.
AB Twenty-four patients infected with human immunodeficiency virus type 1 (HIV-1) who had CD4+ counts of 0.2-0.5 x 10(9) cells/l received granulocyte-macrophage colony-stimulating factor (GM-CSF) in combination with zidovudine plus escalating doses of daily subcutaneous interferon-alpha. Mean neutropenia-inducing doses of interferon-alpha were 9.4 x 10(6) and 10.6 x 10(6) IU/day for groups receiving 100 or 200 mg zidovudine every 4 h, respectively. Mean GM-CSF doses used to reverse neutropenia were 0.64 and 0.63 microgram/kg/day for these two groups, respectively, although the mean minimum effective GM-CSF dose for both was only 0.30 microgram/kg/day. Serum p24 antigen declined greater than 70% in all 5 antigenemic patients. Toxicities included a dose-dependent increase in lymphokine-like side effects (100%), anorexia and weight loss (42%), fatigue (42%), and anemia (50%). While toxicities of the combination can be significant, low-dose GM-CSF readily ameliorated neutropenia associated with zidovudine and interferon-alpha therapy without adversely affecting the antiviral properties of the combination.

L12 ANSWER 11 OF 12 MEDLINE
AN 91073284 MEDLINE
TI A phase I study of recombinant human interferon-alpha 2a or human lymphoblastoid interferon-alpha n1 and concomitant zidovudine in patients with AIDS-related Kaposi's sarcoma.
AU Fischl M A; Uttamchandani R B; Resnick L; Agarwal R; Fletcher M A; Patrone-Reese J; Dearmas L; Chidekel J; McCann M; Myers M
SO JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES, (1991) 4 (1) 1-10. Journal code: 8812597. ISSN: 0894-9255.
AB To determine the safety, maximum tolerated dose, and preliminary efficacy of concomitant interferon-alpha and zidovudine therapy in AIDS-related Kaposi's sarcoma (KS), 56 patients with biopsy-proven KS and documented human immunodeficiency virus type 1 (HIV) infection were enrolled into a phase I study. Interferon-alpha was given intramuscularly at a dose of 9, 18, or 27 mu once a day and zidovudine was administered as 100 or 200 mg every 4 h for 8 weeks followed by a 48-week maintenance period. The major toxicities were anemia, neutropenia, and hepatotoxicity. Neutropenia was dose

limiting with 1,200 mg of zidovudine/day and the lowest dose of interferon-alpha (9 mu/day). Hepatotoxicity was dose limiting with 27 mu of interferon and 600 mg of zidovudine/day. Cumulative dose-related anemia or neutropenia was not seen during long-term follow-up. The maximum tolerated doses for the combination were defined as 18 mu daily for interferon-alpha and 600 mg daily for zidovudine. Variable changes in CD4 lymphocytes occurred during the first 8 weeks of therapy. At higher doses of the combination, sustained increases in median CD4 lymphocyte numbers were noted (p less than 0.001). In HIV antigenemic patients, progressive antigen suppression was seen with increasing doses of the combination (p less than 0.005). The overall antitumor response rate was 47%. Tumor regression was associated with better survival benefits (p less than 0.001) and a pretreatment CD4 cell count greater than or equal to 200 cells/mm3 (p = 0.01). In conclusion, intermediate doses of interferon-alpha and lower doses of zidovudine appear to be relatively well tolerated and associated with disease improvement, including survival benefits.

L12 ANSWER 12 OF 12 MEDLINE
AN 90262043 MEDLINE
TI Interferon-alpha with zidovudine: safety, tolerance, and clinical and virologic effects in patients with Kaposi sarcoma associated with the acquired immunodeficiency syndrome (AIDS).
AU Krown S E; Gold J W; Niedzwiecki D; Bundow D; Flomenberg N; Gansbacher B; Brew B J
SO ANNALS OF INTERNAL MEDICINE, (1990 Jun 1) 112 (11) 812-21. Journal code: 0372351. ISSN: 0003-4819.
AB OBJECTIVE: To evaluate safety, tolerance, and potential efficacy of interferon-alpha and zidovudine combination therapy in patients with Kaposi sarcoma and the acquired immunodeficiency syndrome (AIDS). DESIGN: Open, phase-I study with randomization between two preparations of interferon-alpha. SETTING: Outpatient clinic of a cancer research center. PATIENTS: Forty-three patients with Kaposi sarcoma associated with AIDS. INTERVENTIONS: Patients were treated with interferon-alpha, 4.5, 9, or 18 million U/d, and zidovudine, 100 or 200 mg orally every 4 hours. MEASUREMENTS AND MAIN RESULTS: Neutropenia was the major dose-limiting toxicity. Fatigue, liver enzyme elevation, anemia, and thrombocytopenia were dose-limiting in some patients. Maximum tolerated dosages for interferon-alpha 2a with zidovudine, respectively, were 4.5 million U/d with 200 mg every 4 hours or 18 million U/d with 100 mg every 4 hours. An interferon-alpha n1 [corrected] dosage of 9 million U/d with zidovudine dosages of either 100 or 200 mg every 4 hours induced dose-limiting toxicity in most patients. Of 37 evaluable patients, 17 (46%; 95% CI, 30% to 62%) showed complete or partial tumor regression. Antitumor effects occurred more frequently in patients with baseline CD4 counts above 200 x 10(6) cells/L (65%) than in patients with lower baseline counts (30%, P = 0.05). Effects on CD4 cells were related to both initial CD4 count and interferon dose. Increased skin test reactivity and decreased serum human immunodeficiency virus (HIV) p24 antigen and virus recovery from blood cells were seen. CONCLUSIONS: Combined therapy with interferon-alpha and zidovudine can be safely administered to patients with AIDS and Kaposi sarcoma. The observed effects on tumor growth, HIV replication, and immune function support further studies of the combination in patients at various stages of HIV infection.

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